Metal-catalysed synthesis in the presence of boronates

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The chess-board is the world: the pieces are the phenomena of the universe; the rules of the game are what we call the laws of nature. The player on the other side is hidden from us. We know that his play is always fair, just and patient. But also we know, to our cost, that he never overlooks a mistake, or makes the smallest allowance for ignorance.

By Thomas Henry Huxley

Contents

Acknowledgments

As the graduation is driving near, I would like to thank my supervisors Professor Jonathan Williams and Professor Tony James for giving me this opportunity to do a PhD. In the past three years, you gave me lots of advice and help me solve problems patiently. Your encouragements really helped me make progress. On the voyage of life, you have kindled the light of hope for me. What you have done enriches my mind and broadens my view. On this day I honour you sincerely.

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Finally, a big thank you to my parents, especially my mother Mrs Nan Qiu. She is a great mother and I will not live up to her expectations. I would like to dedicate this thesis to my mother for her love and support.

Abbreviations

Å	Angstrom
Abs.	Absolute
acac	Acetylacetone
anhyd.	Anhydrous
Ar	Aryl group
atm	Atmospheres
Bn	Benzyl
Bz	Benzoyl
b.p.	Boiling point
Boc	*t*-butyloxycarbonyl
c	Concentration
COD	1,5-Cyclooctadiene
Cp*	Pentamethylcyclopentadienyl
dippf	1,1'-Bis(diisopropylphosphino)ferrocene
DMF	*N*,*N*-Dimethylfomamide
DMSO	Dimethylsulfoxide
DPEphos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppe	1,1'-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,1'-Bis(diphenylphosphino)propane
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray Ionisation
Et	Ethyl
Et_3N	Triethylamine
EtOH	Ethanol
GLC	Gas-liquid chromatography

h	Hours
HPLC	High pressure liquid chromatography
Hz	Hertz
i	*Iso*
iPr	*iso*-propyl
J	Coupling constant
KOtBu	Potassium *tert*-butoxide
LC	Liquid Chromatography
M	Molar
m.p.	Melting point
Me	Methyl
MeCN	Acetonitrile
MHz	Megahertz
min	Minute
MS	Molecular sieves
MW	Microwave
$NaBH_4$	Sodium borohydride
$NaCNBH_4$	Sodium cyanoborohydride
NMR	Nuclear Magnetic Resonance
p	*Para*
PCy_3	Tricyclohexyl phosphine
Ph	Phenyl
p*K*a	Acid dissociation constant
PPh_3	Triphenyl phosphine
Pr	Propyl
rac	Racemic
r.t.	Room temperature
RBF	Round-bottom Flask
t	*Tert*

tBu	*tert*-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
UV	Ultraviolet
wt.	Weight
δ	Chemical shift

Abstract

The work described in this thesis was carried out in last three years and is the original work of the author except where indicated by appropriate reference of acknowledgment.

This thesis describes the use of alcohols as alkylating agents for the formation of new C-C and C-N bonds and the development of new, advantageous, catalytic syntheses of boronic acid compounds.

Chapter 2 describes in particular the ruthenium-catalysed coupling of a protected boronic acid alcohol and an amine or a protected boronic acid amine and an alcohol by “borrowing hydrogen”.

Chapter 3 describes how this process can be applied to the synthesis of a range of boronic acid molecular sensors, providing an alternative to the traditional methods which use mutagenic alkyl halides as the alkylating agents.

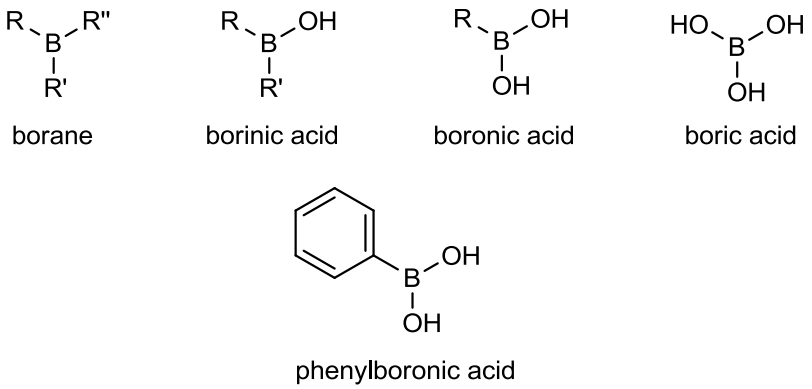
Chapter 4 describes the development of catalytic syntheses of amide bonds. The development of a copper-catalysed rearrangement of aldoxime boron compounds into primary boronic amides is discussed, followed by the development of an efficient catalysed coupling of aldehydes and amines

1. Introduction

Boronic acids are used extensively in organic chemistry as chemical building blocks and their derivatives are the most useful classes of organoboron molecules. Boronic acids are an important building block for saccharide sensing and the molecular recognition of saccharides is a major area of sensing. Boronic acid sensors can be used in medical applications for the diagnosis of diabetes or the detection of pathogens and cancer. An introduction of some methods concerning the synthesis of amines is given. Amines are one of the most common compound classes in organic chemistry and most of them are ammonia derivatives. The last section introduces direct coupling methods, non-metal catalysts, metal catalysts and enzymatic methods that are used for amide formation.

1.1 Introduction to Boronic Acids

Boronic acids are very useful building blocks for organic synthesis. The first isolation of a boronic acid was reported by Frankland and published by the Royal Society of Chemistry of London in 1860.[1] The highly air-sensitive triethylborane was obtained by treating diethylzinc with triethylborate, and it would slowly oxidise in a normal atmosphere environment to provide ethylboronic acid. Boronic acids are the products of the second oxidation of boranes. The product of the first oxidation produces a borinic acid and the third oxidation is boric acid. Boronic acids are more stable than borinic acids, but less stable than boric acid. Soon afterward, the first synthesis of phenylboronic acid was performed by Michaelis and Becker in 1880.[2] Boron trichloride was reacted with diphenylmercury to form dichlorophenylborane, and then hydrolysed to phenylboronic acid and recrystallised as colourless needles (Scheme 1.1).

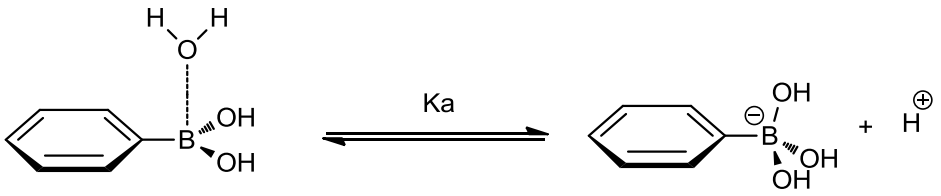


Scheme 1.1. *Organoboron compounds*

From 1911 to 1940, Böeseken and co-workers discovered that boric acid complexes with hydroxyl groups in solution, favourably forming boronic ester 1,2- or 1,3-diol configuration. A rise was also observed in both conductivity and pH. In 1954, Kuivila and co-workers found the formation of a cyclic boronic ester by adding phenylboronic acid to a solution of mannitol, similar to the formation between boric acid and polyols.[3]

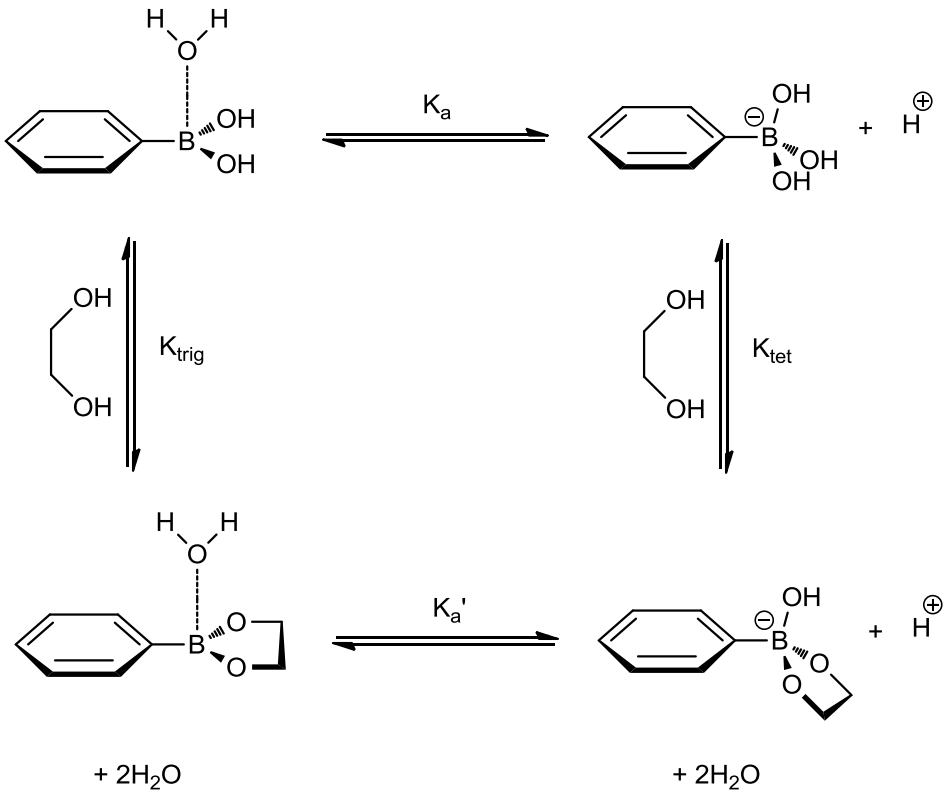
Figure 1.1. *The planar structures of boric acid and phenylboronic acid.*

In 1959, in an experiment by Lorand and Edwards, different polyols were added to a solution of phenylboronic acid to clarify the structure of the phenylboronate anion. They inferred that the conjugate base of phenylboronic acid has a tetrahedral structure rather than a trigonal form. Because the pH is matching with the pK_a, the pK_a of the boronic acid can only be measured from the interaction of the boron atom with a molecule of water where the dissociation of a hydrogen ion from phenylboronic acid occurs. The pK_a of phenylboronic acid was initially reported to fluctuate between 8.7 and 8.9 by several papers and later defined *via* a potentiometric titration study as 8.7 in water at 25 ^{0}C.[4]



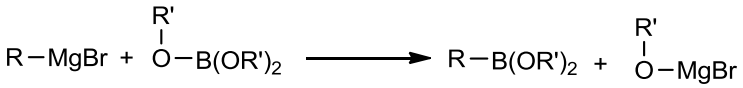
Scheme 1.2. *The acid – conjugate base equilibrium for phenylboronic acid in water.*

The neutral boronic acid and the equivalent boronate ester both bind with diols in aqueous solution. The acid – conjugate base equilibrium for phenylboronic acid in water can be further described in a thermodynamic cycle. The acidity constant of the unbound neutral boronic acid complex is defined as K_a and the acidity constant of the bound complex is defined as K_a', where it is shown that $K_a > K_a'$. This is caused by the bound boronic acid complex becoming more acidic after binding with a diol. From Scheme 1.3 below, the formation of the diol-boronate anion complex is defined as K_{tet} and the diol-boronic acid complex is defined as K_{trig}. It was shown that $K_{tet} > K_{trig}$.[5]



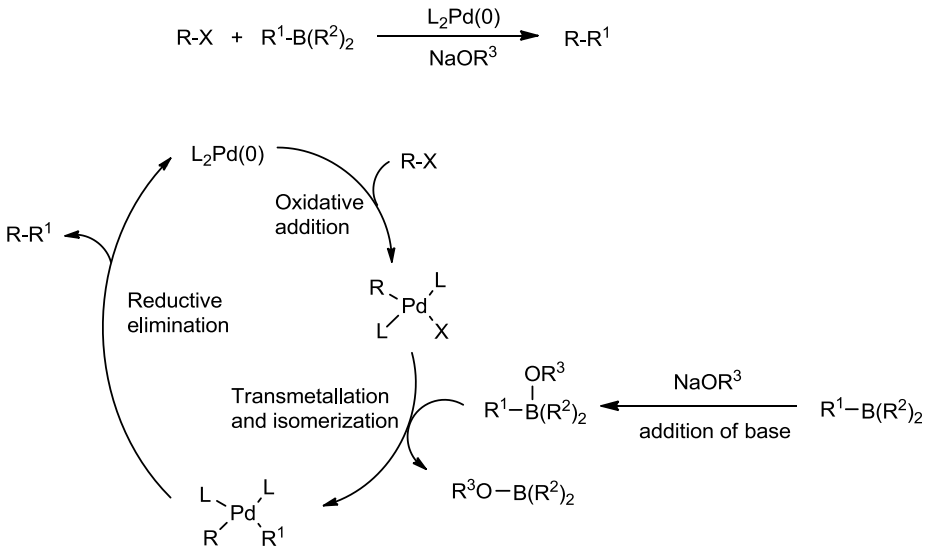
Scheme 1.3. *The equilibrium for boronate ester formation to generate a thermodynamic cycle*.

In 1909, the classical synthesis of boronic acids from Grignard reagents and trialkyl borates was established (Scheme 1.4).[6]



Scheme 1.4. *The classical synthesis of boronic acid*

In the late 20th century, the Suzuki-Miyaura coupling reaction was developed for C-C bond formation, using a palladium catalyst and boronic acid with a halide or triflate (Scheme 1.5).[7]



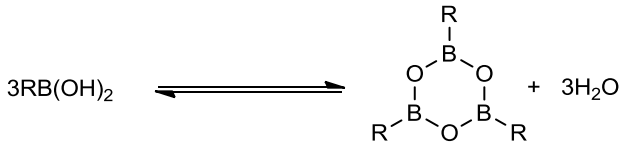
Scheme 1.5. *Suzuki coupling catalytic cycle.*

The Suzuki cross-coupling reaction, as well as the Kumada, Negishi, Stille and Hiyama cross-coupling reactions, belong to a category of Pd-catalysed cross-coupling reactions of organic halides, triflates and other electrophiles with organometallic reagents.[8] Oxidative addition of the halide compound to the palladium(0) complex forms a palladium(II) intermediate which then undergoes transmetallation and isomerisation with the boronate compound, and finally the product is generated by reductive elimination.

In the late 20th century, the first boronic acid drug was synthesised using a rhodium catalysed coupling with alkenes and aldehydes, and used in human health therapy, and since then the number of publications focused on boronic acids has increased rapidly.[9] Moreover, because most boronic acids compounds exhibit low toxicity and degrade into relatively non-toxic boric acid, boronic acids can be regarded as “green” reagents.[10]

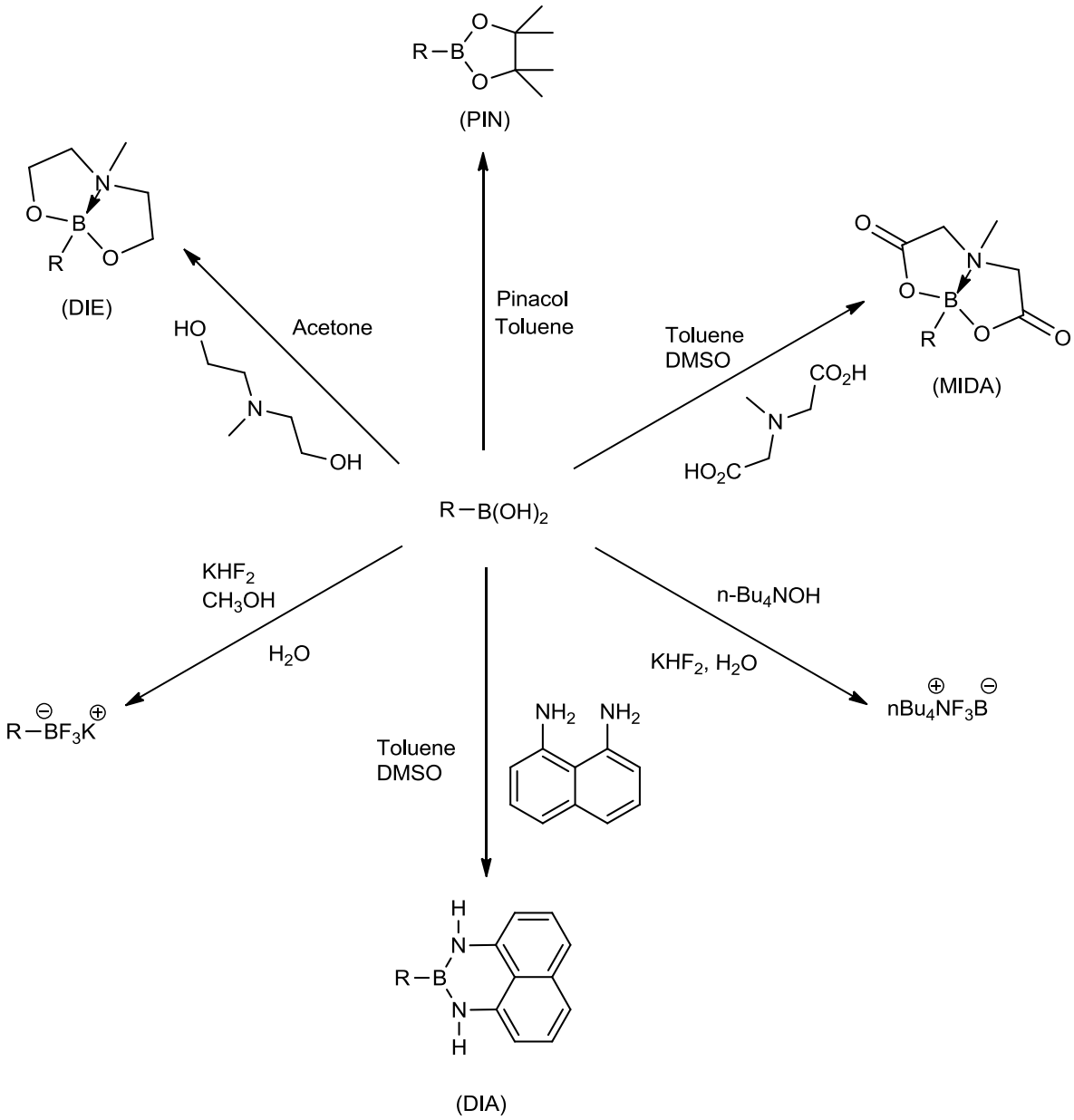
Although now thousands of boronic acids have been made, most of these boronic

acid compounds are very difficult to purify. There are two major problems; the first is that free boronic acids are complicated by the equilibrium formation of boroxines (trimeric cyclic anhydrides, Scheme 1.6).[11]



Scheme 1.6. *Boronic acid equilibrium*

Due to this problem, it is very difficult to determine the percentage of boronic acid and boroxine in a mixture. Therefore, most of the Suzuki-Miyaura coupling reactions and some similar reactions need to use excess boronic acids to ensure a complete reaction. Secondly, boronic acids strongly interact with silica gel making chromatographic purification problematic. In order to avoid these problems, many different kinds of protecting group are used in reactions to protect the free boronic acid before starting the main reaction (Scheme 1.7).[12]



Scheme 1.7. *Examples of boronic acid protecting groups*.

1.2 Introduction to Amines

Most basic amines are derived from alkaloids which exist in nature. Morphine was the first individual alkaloid, isolated from opium poppy in 1804.[13] Some representative alkaloids like Colchicine **1.1**, Caffeine **1.2** and Nicotine **1.3** are shown in Figure 1.2 and their basic nature can produce a strong physiological activity.[14]

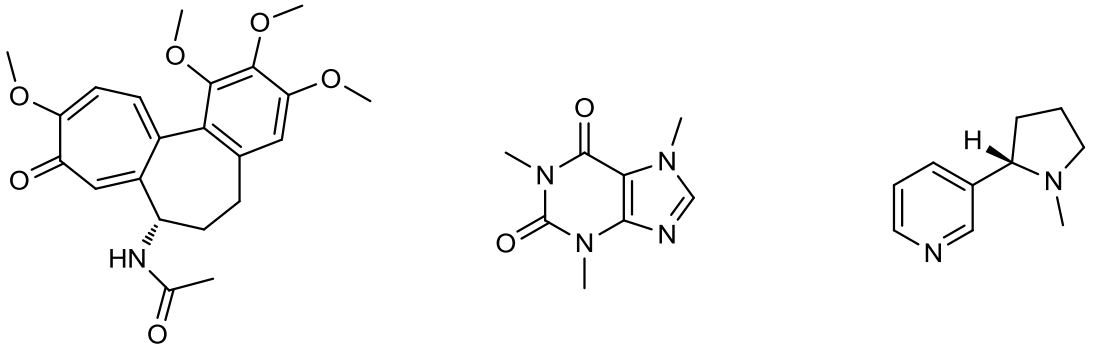
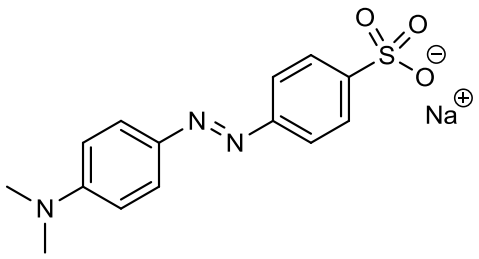
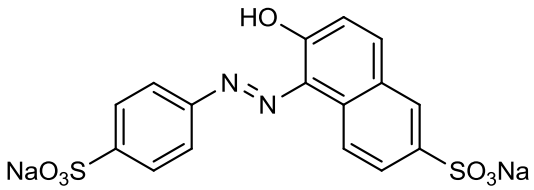


Figure 1.2. *Structures of some representative alkaloids.*

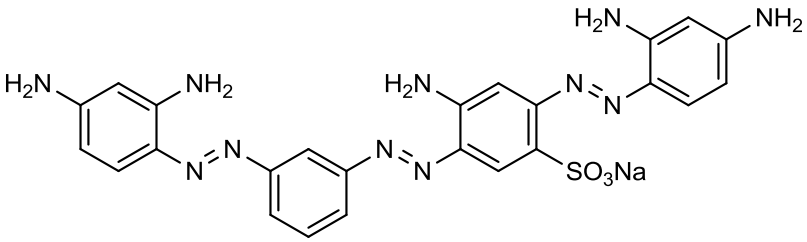
Amines are very important organic compounds and functional groups in chemistry. In the industry, amines can be prepared from ammonia by alkylation with alcohols. There are also lots of methods to prepare amines on a laboratory scale, such as Hofmann degradation, the Buchwald-Hartwig reaction and aminolysis of halides. Amines are fundamental starting materials for many organic syntheses to create new compounds. Comparing aliphatic amines with aromatic amines, the aromatic amine is more reactive due to an electron donating effect from the aromatic ring. Aniline is one kind of primary aromatic amine which is the basis for the synthesis of a whole class of synthetic dyes (Figure 1.3).[15]



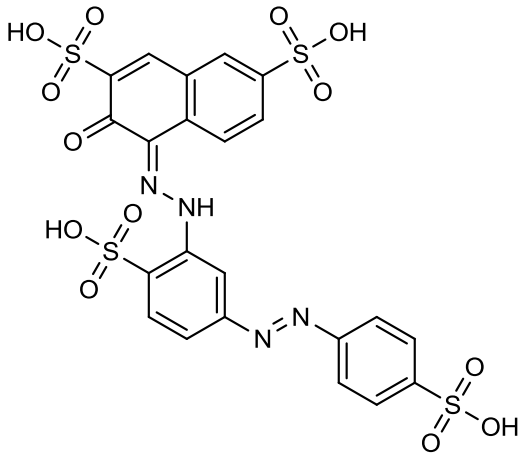
Methyl orange



Sunset yellow FCF



Direct Brown 138



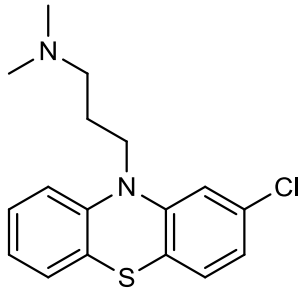
Ponceau S

Figure 1.3. *Structures of some representative dyes.*

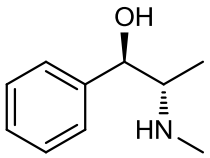
Primary aromatic amines can react with nitrous acid to form a diazonium salt. The diazonium salt can do a further coupling reaction to form azo compounds which are used industrially as dyes.

Lots of drugs and biological compounds are designed to imitate or interfere with the natural action of amines. Many of them have a strong physiological activity and

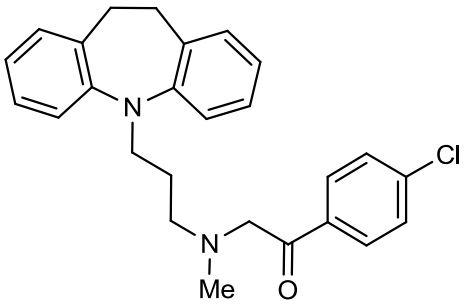
others have been widely used in biological products such as antihistamines, neurotransmitters and antidepressants. Chlorpromazine **1.4** was first synthesised in 1950. It was the first antipsychotic drug for the treatment of mental illness and it has made the rapid development of psychopharmacology possible.[16] Ephedrine **1.5** is a sympathomimetic amine. It is often used as a stimulant, to relieve nasal congestion, an appetite suppressant and anasthetic.[17] Lofepramine **1.6** was first synthesised in 1983 and it is used for treatment of depression. It is a sedative and the antimuscarinic effect is weaker.[18] Chlorphenamine **1.7** is used in allergy medication and Dopamine **1.8** is found in the brains of most animals.[19] It can affect a person's sentiment and Carlsson was awarded the 2000 Nobel Prize in Medicine for showing that dopamine is an important neurotransmitter in the brain.[13]



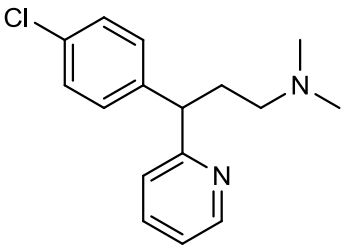
1.4
Chlorpromazine



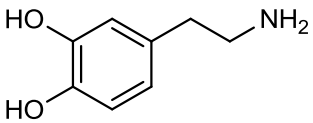
1.5
Ephedrine



1.6
Lofepramine



1.7
Chlorphenamine



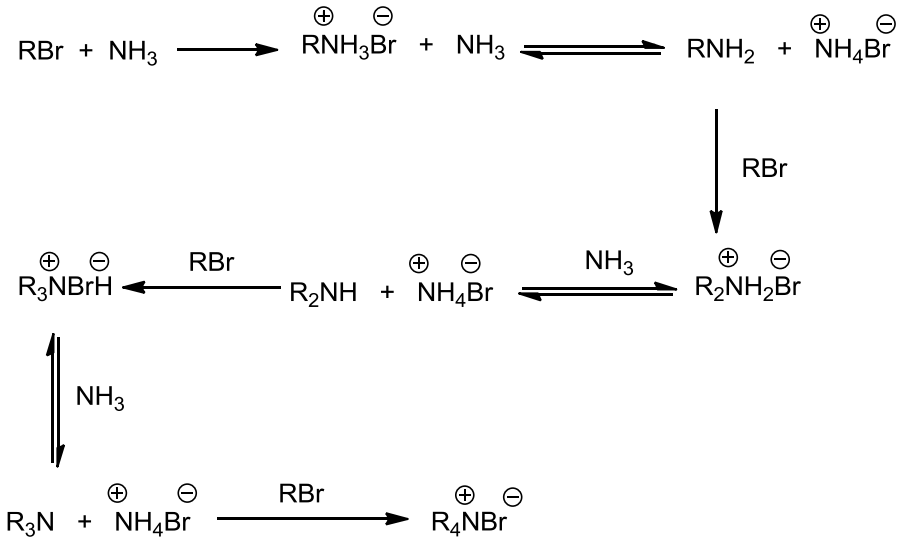
1.8
Dopamine

Figure 1.4. *Some medicinally important amines.*

Amines are also used in the preparation of some solvents, fine chemicals and are used in the agrochemical industry. In general, amines are naturally occurring compounds of biological activity present in large number of compounds and are thus important intermediates in the chemical industry.

1.2.1 Amine formation

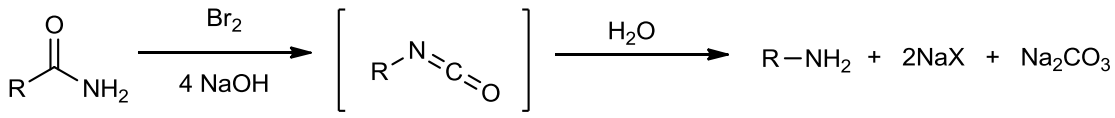
Amines can be made from halogenoalkanes when heated in ethanol with a concentrated solution of ammonia.[20] However, excessive alkylation can lead to a mixture of primary, secondary, tertiary amines and quaternary ammonium salts in the final products (Scheme 1.8). This causes the purification of the product to be difficult and the method is very expensive.



Scheme 1.8. *Overalkylation of amines.*

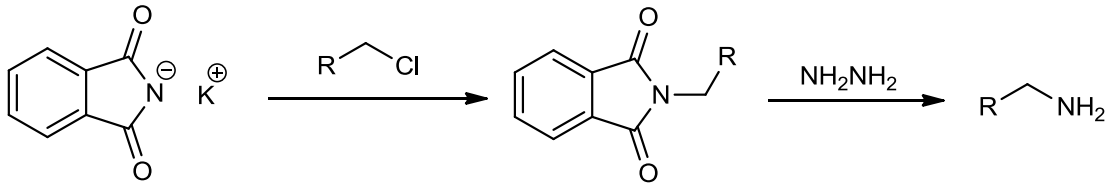
The overalkylation of amines is wasteful and expensive. In 1881, an organic reaction was discovered by August Wilhelm von Hofmann to create a primary amine from a

primary amide. (Scheme 1.9) In the reaction, bromine reacts with sodium hydroxide first to form sodium hypobromite which can react with the primary amide to form an intermediate isocyanate. The isocyanate can be hydrolysed by H_2O to form the primary amine.[21]



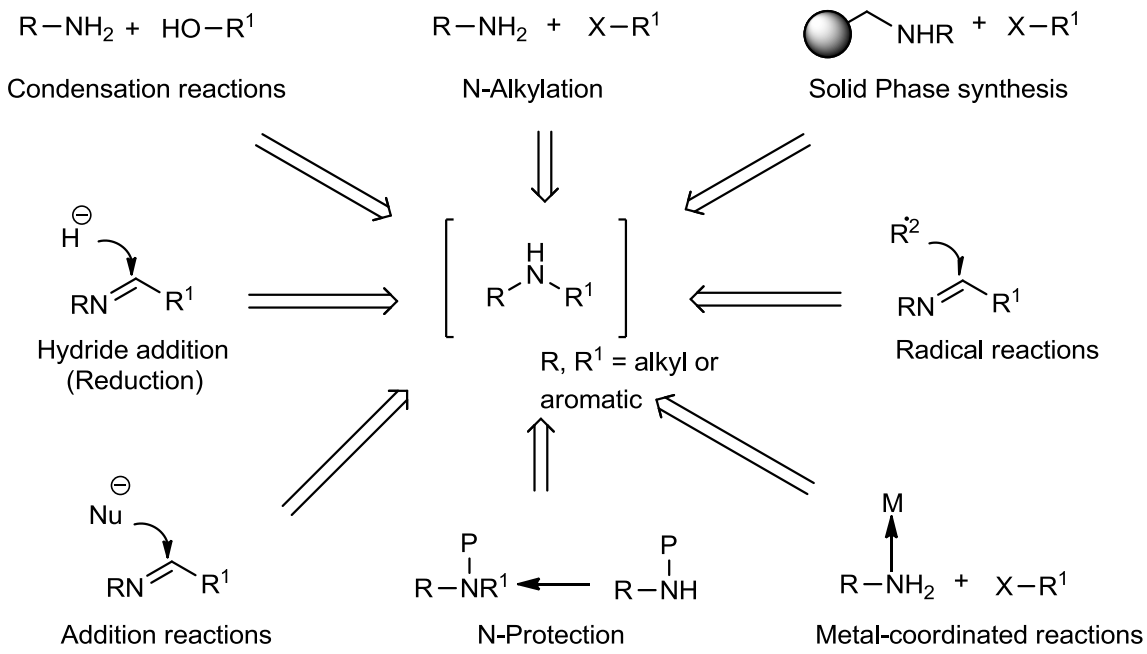
Scheme 1.9. *Hoffman rearrangement.*

In 1887, another method for the generation of primary amines was developed by a German chemist Siegmund Gabriel (Scheme 1.10). In the Gabriel synthesis, potassium phthalimide is reacted with a primary alkyl-halide to give the corresponding *N*-alkylphthalimide. The *N*-alkylphthalimide can be hydrolyzed by aqueous base or acid into the primary amine.[22]



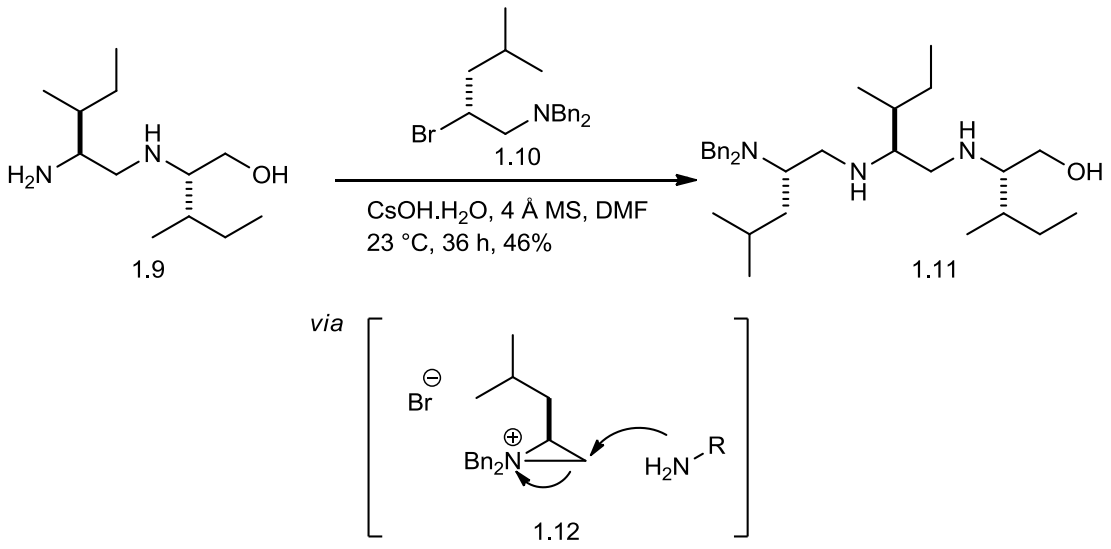
Scheme 1.10. *Gabriel synthesis.*

It is also very important to find efficient synthetic methods to prepare secondary amines as they are particularly important in the area of drug discovery. Traditional methods of forming secondary amines have different problems, such as low chemical selectivities, very poor yields and difficult reaction conditions. In Scheme 1.11, there is a brief classification of some traditional methods for making secondary amines as described by Salvatore.[23]



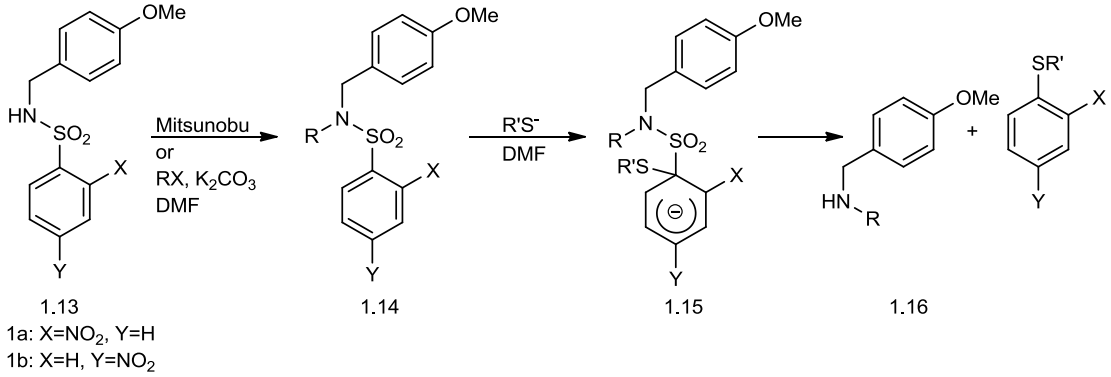
Scheme 1.11. *Major traditional methods for the synthesis of secondary amines.*

Salvatore and co-workers also developed a method using cesium bases in DMF for the mono-*N*-alkylation of primary amines, diamines and polyamines, efficiently preparing secondary amines (Scheme 1.12). The free primary amines of dimer **1.9** reacted with protected amino bromide **1.10** selectively leaving secondary amine and hydroxyl untouched, indicating the high chemoselectivity and diminished reactivities of secondary amines. This formed product **1.11** cleanly, proceeding though an aziridinium intermediate **1.12**. Advantages of this method are mild reaction conditions and the possible application in generating large compound libraries, but it is limited to the syntheses of non-aromatic amines.[24]



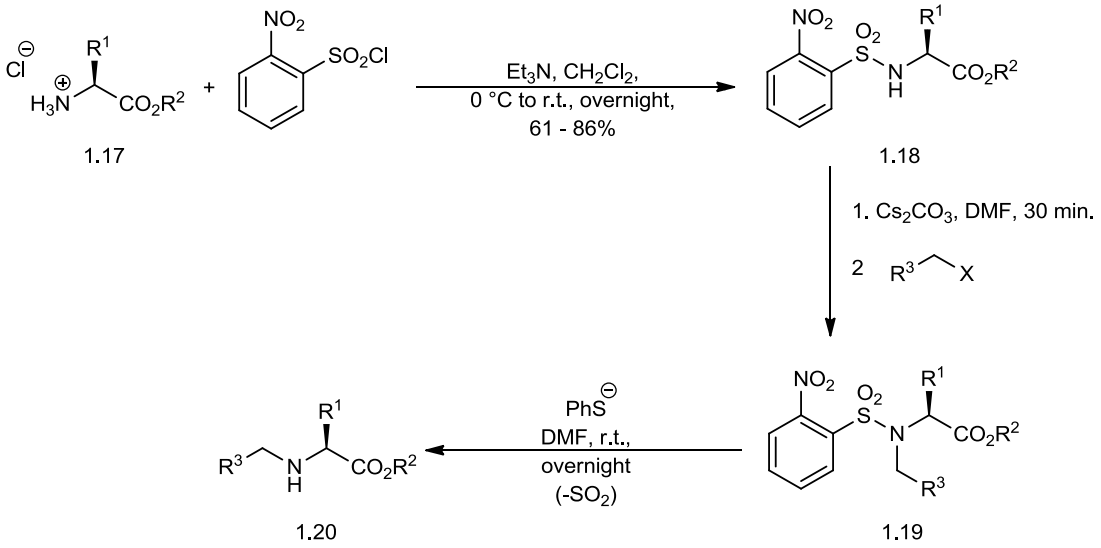
Scheme 1.12. *CsOH-promoted N-alkylation of dimer **1.9** with protected amino bromide **1.10** to afford trimer **1.11** cleanly via aziridinium intermediate **1.12**.*

Fukuyama and co-workers introduced the 2-nitrobenzenesulfonyl group which can be used as an amine protecting group and reacts with thiolates in DMF at room temperature to give secondary amines in high yields. As shown in Scheme 1.13, amide **1.14** can be prepared from starting amide **1.13** under Mitsunobu conditions or under the more general base mediated conditions (RX, K_2CO_3, DMF in 23 °C). Treating amide **1.14** with PhSH and K_2CO_3 in DMF at 23 °C gives the target secondary amine **1.16** in good yield, *via* the Meisenheimer complex intermediate **1.15**.[25]



Scheme 1.13. *Preparation of secondary amines and protection of amines.*

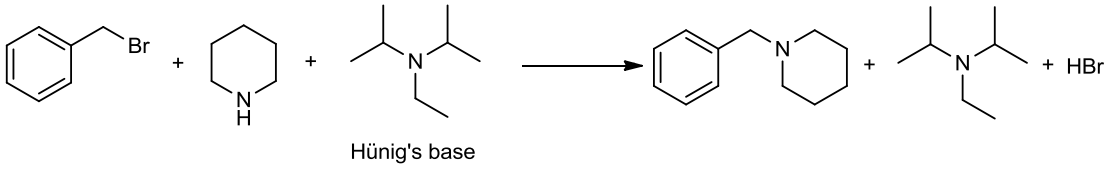
In 1997, Bowman and co-workers reported monoalkylation of the amino group using α-amino esters facilitated using 2- or 4-nitrophenylsulfonamide as a protecting group, with removal of the nitrophenylsulfonyl group giving the *N*-alkylated α-amino acid. In an ice-cooled solution, amine **1.17** reacts with 2-nitrobenzenesulfonyl chloride (NsCl) and NEt_3 to generate the corresponding sulphonamide **1.18**. Intermediate **1.19** can be created by using Cs_2CO_3 and subsequent alkylation with sulfonamide **1.18**. Removal of the sulfonyl group by using a phenylthiolate anion generates the corresponding final product *N*-monoalkylated α-amino acid **1.20**.[26]



1.17 1.18 1.19 1.20

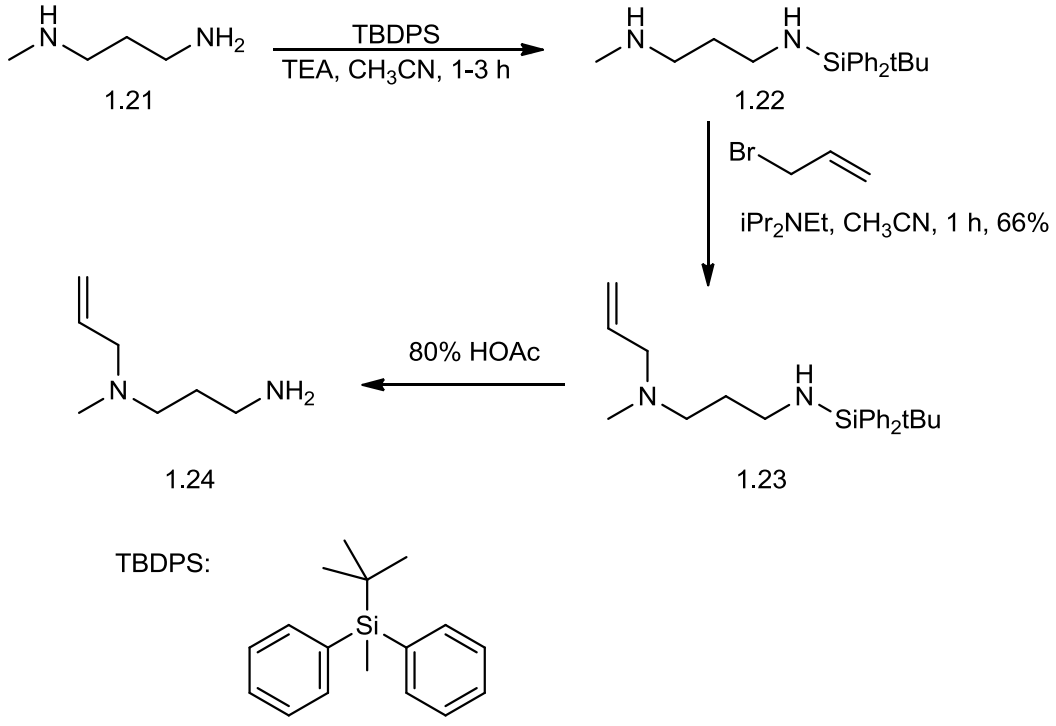
Scheme 1.14. *N-alkylation of α-amino acids.*

The *N*-alkylation of primary and secondary amines with alkyl halides in the presence of base is the most common and useful procedure for the synthesis of tertiary amines. Hünig's base (*N*,*N*-diisopropylethylamine) has been found to act as a selective reagent for the direct formation of tertiary amines *via* *N*-alkylation of secondary amines by alkyl halides in acetonitrile. This organic reaction is usually complicated by the generation of quaternary ammonium salts, but these side-products can be reduced when Hünig's base is present.[27]



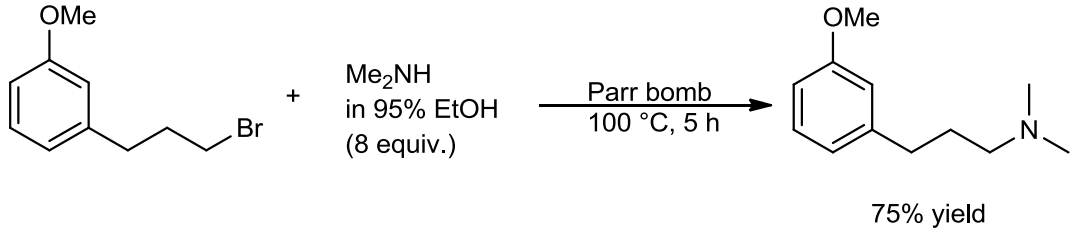
Scheme 1.15. *Direct alkylation of a secondary amine with an alkyl halide in the presence of Hünig's base.*

As demonstrated by Overman, the TBDPS group is able to selectively functionalise secondary and tertiary amines in the presence of primary amines. Diamine **1.21** is easily silylated at the primary amine to generate silyamine **1.22**. Silyamine **1.22** can undergo direct formation of tertiary amine **1.23** *via N*-alkylation by using 1 equivalent of allyl-bromide and 10 equivalents of diisopropylethylamine in acetonitrile. Finally, acetic acid (80% HOAc) is used to deprotect and generate product **1.24** (Scheme 1.16).[28]



Scheme 1.16. *TBDPS group selective functionalization of a tertiary amine.*

The traditional method for the synthesis of dimethylamines is the *N*-alkylation of an excess amount of dimethylamine with alkyl halides at high temperatures and pressure, an example of which is shown in Scheme 1.17.[29]



Scheme 1.17. *N-alkylation of Me_2NH with an alkyl halide.*

1.3 Boron – Amine Interactions

In the past 100 years, there have been a large number of studies focused on nitrogen-boron bonding. Electron-donating groups can increase the Lewis basicity of nitrogen and electron-withdrawing groups can increase the Lewis acidity of boron, so the strength of nitrogen boron bonds is dependent on the substituents at both of these atoms. Examples of this are shown in Figure 1.5 below, with the pK_a of different boronic acids varying with the electron-withdrawing groups and the electron-donating groups attached to them.[4d, 30]

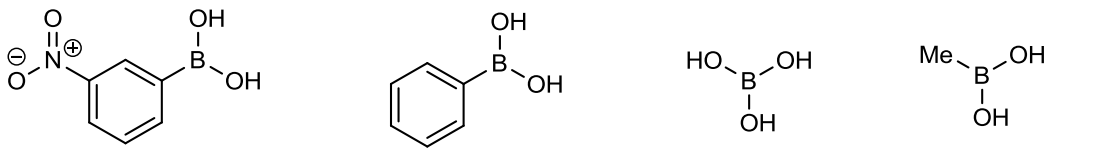
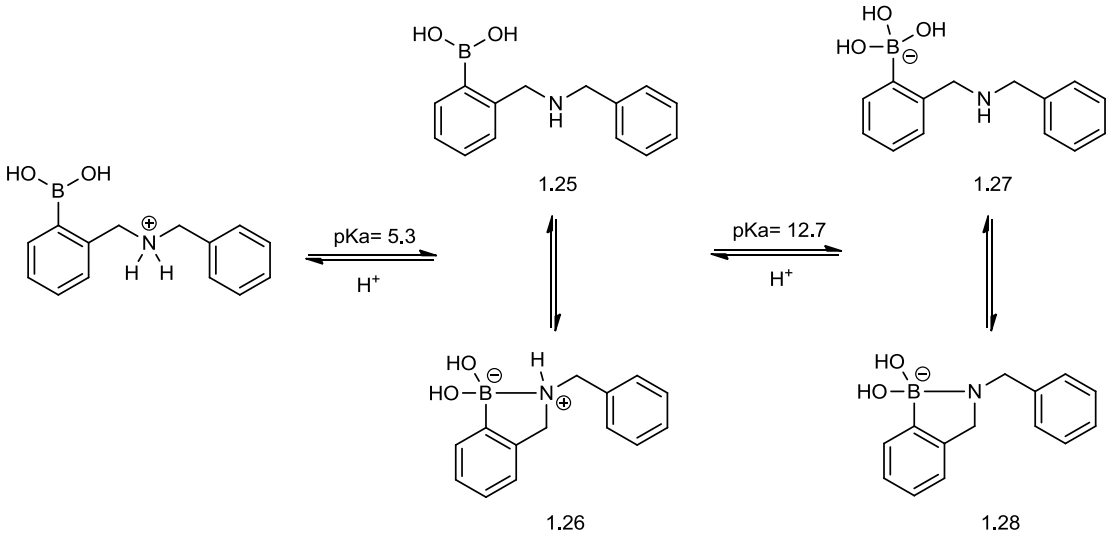


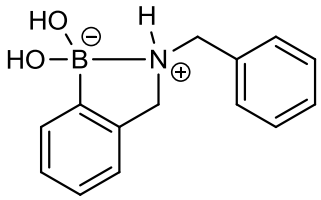
Figure 1.5. *A series of boronic acids with their respective pKa values.*

(2-((Benzylamino)methyl)phenyl)boronic acid was taken as an example by the Wulff, Anslyn and James groups separately (Scheme 1.18).[31] Wulff demonstrated that the lone pair of electrons on the nitrogen would donate into the empty *p*-orbital on the boron, creating tetrahedral sp^3-hybridised boron at or near neutral pH. This is shown in the equilibrium between compounds **1.25** and **1.26** or **1.27** and **1.28**. Bearing progated nitrogen, the ammonium cation species prohibits any N-B interaction. The energy of the nitrogen – boron interaction has been calculated by potentiometric titration as being between 15 and 25 kJ mol^{-1}. Computational analysis estimated the nitrogen – boron interaction to be approximately 13 kJ mol^{-1} or less in the absence of solvent which matches the previous results.[4h, 5]

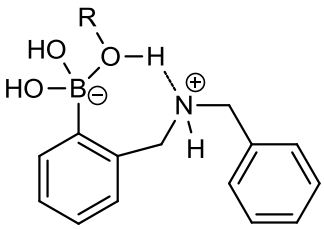


Scheme 1.18. *The extent of the interaction between nitrogen and boron is illustrated within the upper and lower bounds of possible contact depicted as the cyclic and acyclic forms*.

A zwitterionic species can be generated in protic solvent systems and solvent insertion can occur between the nitrogen and boron. In these protic solvent systems, compound **1.29** will form rather than **1.26**.[32]



1.26

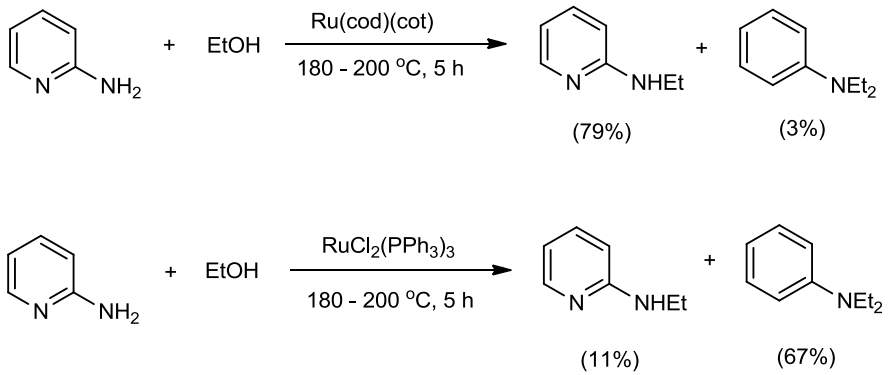


1.29

R = H (H_2O)
R = CH_3 (methanol)

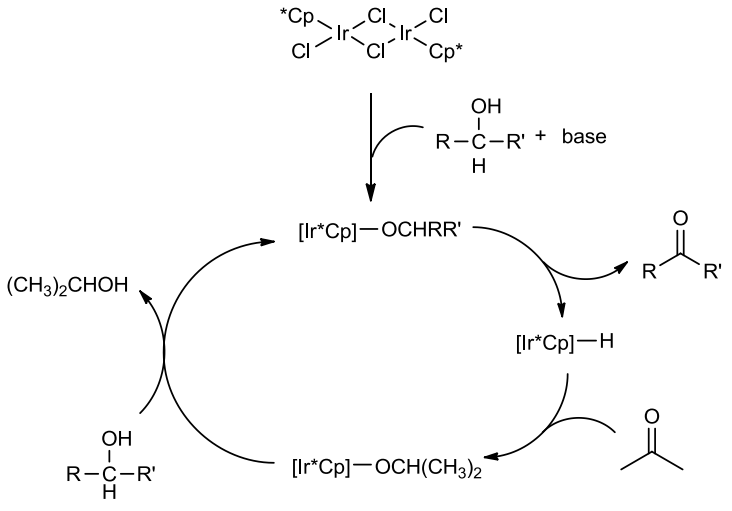
1.4 Borrowing Hydrogen

In recent years a great deal of attention has been focused on the alkylation of amines, particularly the reaction of amines with alkyl halides, and an electrophilic alkylating agent. At the beginning of the 20th century, Sabatier and co-workers reported the first *N*-alkylation of amines with alcohols by using a ThO_2 catalyst. However, alkylation reactions can prove difficult to control as the product of the alkylation may react further.[23] The first homogeneous catalysts towards the amination of alcohols were reported by Grigg and Watanabe in 1981.[33] After that, ruthenium, rhodium, platinum and iridium catalysts have been reported. The disadvantages presented by these catalysts are that high temperature and long reaction times are usually required to obtain optimum yields.[34] In 1996, Watanabe reported the first ruthenium complex-controlled catalytic *N*-mono- or *N*,*N*-dialkylation of heteroaromatic amines with alcohols. In this reaction, the monoalkylated and dialkylated amines can be controlled by using various ruthenium complexes at 150 – 200 °C, such as [Ru(cod)(cot)] and [$RuCl_2(PPh_3)_3$] (Scheme 1.19).[33a]



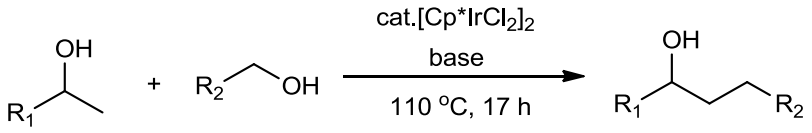
Scheme 1.19. *N-Ethylation of heteroaromatic amines with ethanol using ruthenium catalysts.*

After the first examples of homogeneous ruthenium catalysts for these reactions, further ruthenium complexes have been shown to be active for this transformation. However, iridium catalysts have also proved to be as effective as ruthenium, with several iridium catalysts found to be effective catalysts for the *N*-alkylation reaction of amines with alcohols. Fujita and co-workers have described recent studies on the chemistry of η^5-pentamethylcyclopentadienyl (Cp*) iridium complexes, finding that the $[Cp^*IrCl_2]_2$ catalyst has high catalytic activities and is good for hydrogen transfer. Primary and secondary alcohols can be oxidized using catalytic amounts of $[Cp^*IrCl_2]_2$ and K_2CO_3 in acetone under mild conditions. Compared with many other oxidation methods, this reaction is achieved under mild and less toxic conditions. The possible mechanism is shown in Scheme 1.20.[35]



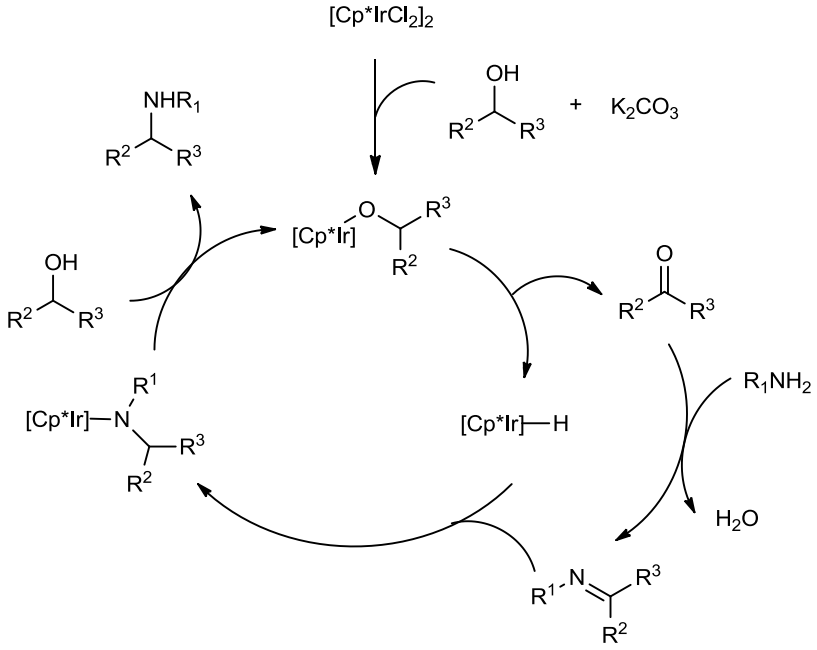
Scheme 1.20. *Possible iridium catalysis mechanism*

They also found the iridium catalyst can be used for carbon-carbon bond formation. Different secondary alcohols can react with various primary alcohols in the presence of $[Cp^*IrCl_2]_2$ and achieve excellent yield without any hydrogen acceptor or donor (Scheme 1.21).[36]



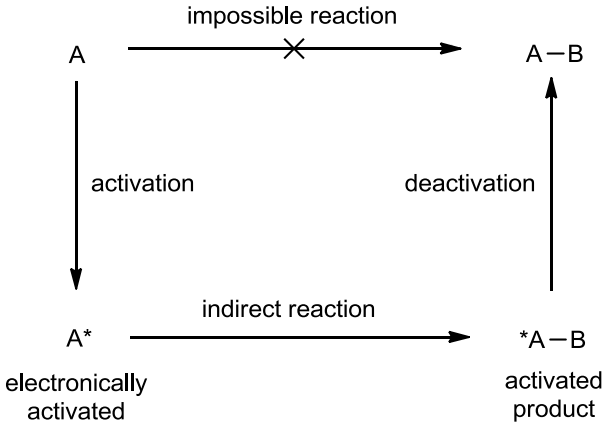
Scheme 1.21. *Carbon-carbon bond formation using iridium catalyst.*

The $[Cp^*IrCl_2]_2$ catalyst can also be used for *N*-alkylation of primary and secondary amines with alcohols. In the reaction, equivalent amounts of the amine and alcohol in the presence of base give carbon-nitrogen bond formation. However, whilst there were good yields in the presence of K_2CO_3 as base, it was found that weak bases were not effective for the reaction. When the reaction was carried out without base, a low yield of 30% was obtained. The possible mechanism for this reaction is shown in Scheme 1.22.[37]



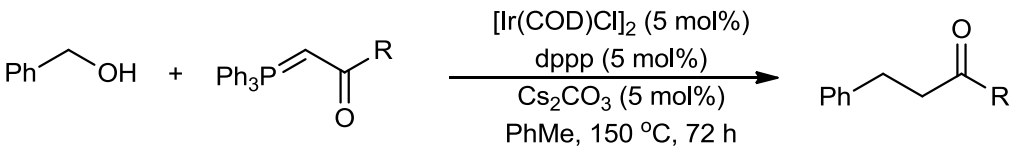
Scheme 1.22. *N-Alkylation of amines with alcohols catalyzed by a Cp*Ir complex.*

The idea of “catalytic electronic activation” has evolved from previous research by the Williams group which “temporarily enhance the electronic nature of a functional group to a given reaction”.[38] They reasoned that if an unreactive substrate **A** could be temporarily activated into electronically activated **A*** towards reaction then the desired bond formation could form the activated intermediate **A***-**B**. By return of **A***-**B** to the initial oxidation level can be yield the desired product **A**-**B**. They termed this concept Catalytic Electronic Activation (Scheme 1.23).[39]

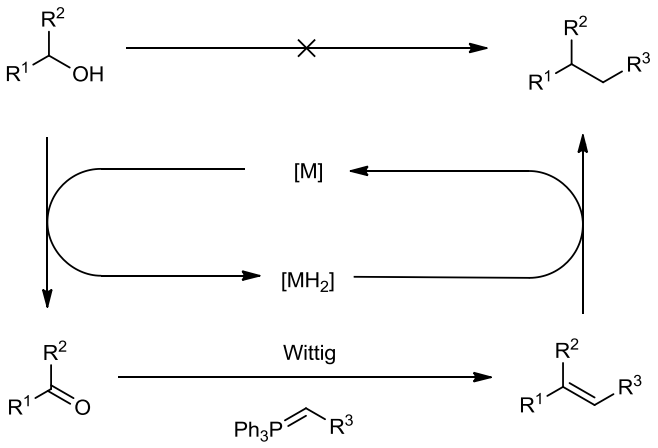


Scheme 1.23. *Catalytic Electronic Activation.*

The concept of catalytic electronic activation is an attractive route to the formation of a new C-C bond.[40] In general, alcohols have a poor reactivity in these reactions and need to be activated, by adding acid (to form an electrophilic species) or base (to form a nucleophilic species). However, there is a pathway to activate alcohols as aldehydes or ketones by using transition metal catalysts in a process named “borrowing hydrogen”.[41] They started to test the “borrowing hydrogen” hypothesis by studying C-C bond formation between alcohol substrates *via* an indirect Wittig reaction (Scheme 1.24).[39]

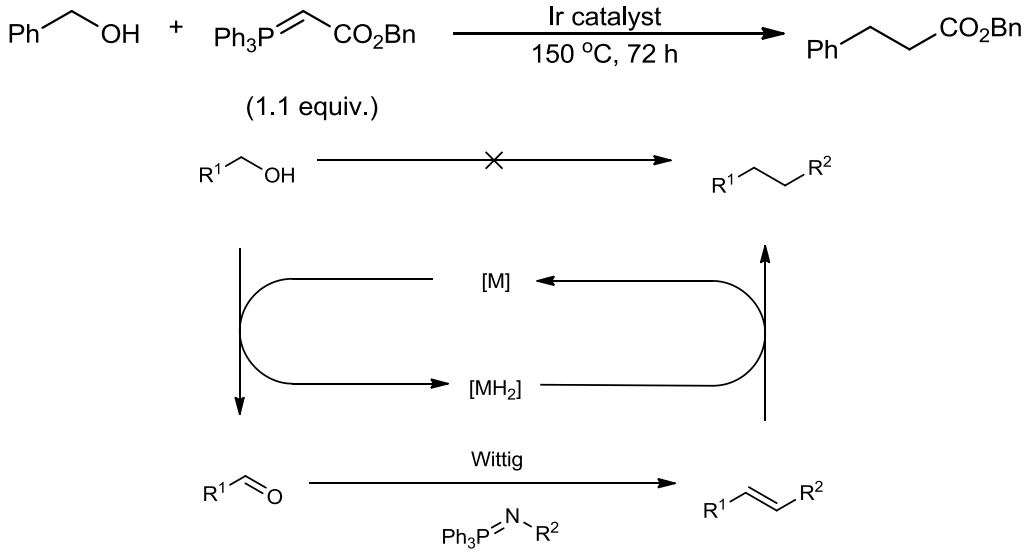


R = OMe or OBn



Scheme 1.24 *Indirect Wittig reaction of alcohol by "borrowing hydrogen".*

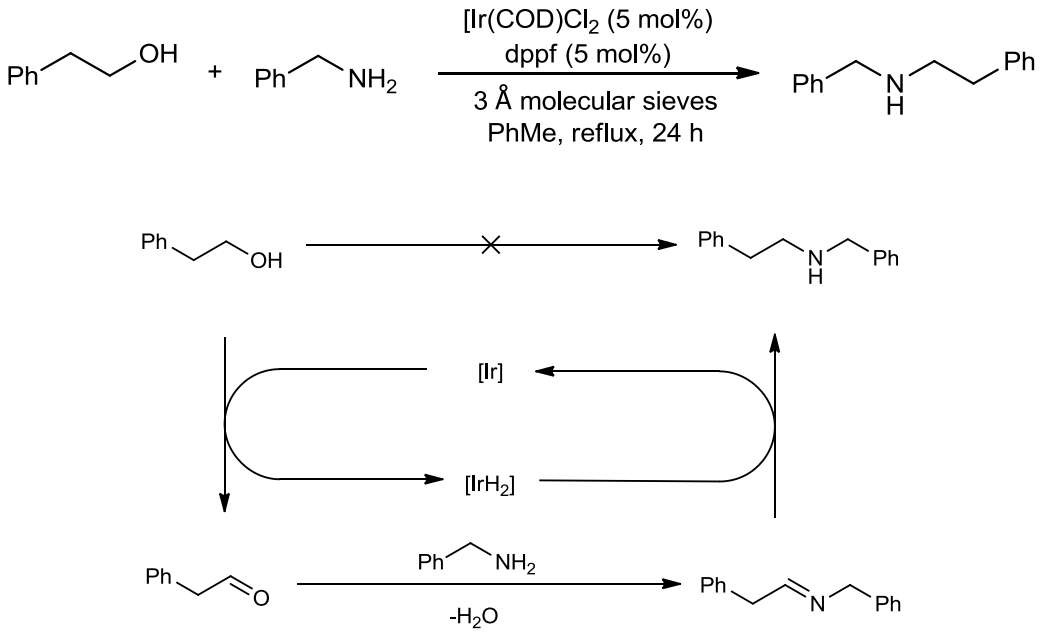
These preliminary findings were reported in 2002 by Williams and subsequently an improved ruthenium-catalysed system that proceeded under mild conditions was reported by the group. They also used the "borrowing hydrogen" for the formation of C-N bonds *via* aza-Wittig and imine chemistry (Scheme 1.25).[42]



Scheme 1.25 *indirect aza-Wittig reactions upon alcohols.*

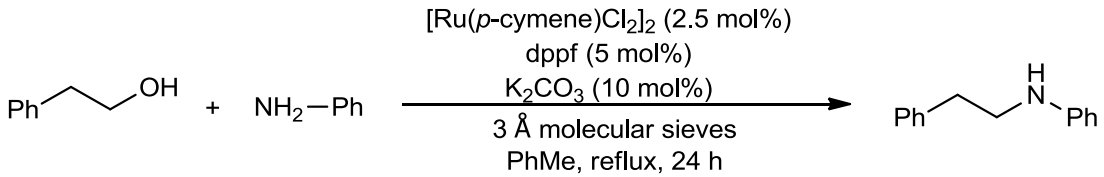
Although this method was successful in the synthesis of new C-N bond, it was very difficult to remove all the triphenylphosphine when the reaction was finished. During the reaction imines are formed between an aldehyde or ketone with an amine with

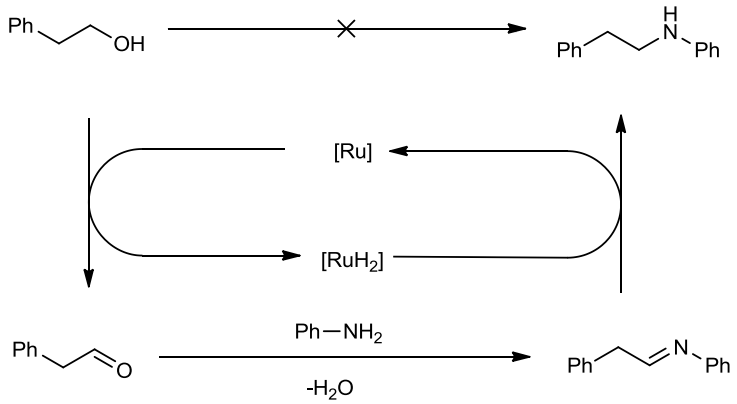
the azeotropic removal of water. Afterwards, the Williams group proposed to use free amines instead of iminophosphoranes and the use of molecular sieves enabled these reactions to achieve high yield (Scheme 1.26).[43]



Scheme 1.26 *N-Alkylation of amines by* Iridium catalysts

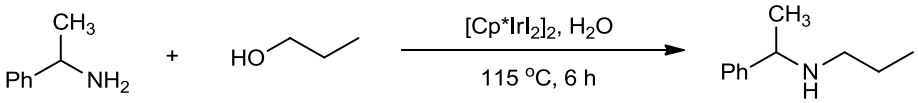
After this method was developed, the Williams group reported that they used alcohols as alkylating agents to react with primary amines to convert them into secondary amines by using $[Ru(p\text{-cymene})Cl_2]_2$ as a catalyst and a bidentate phosphine ligand (Scheme 1.27).[44]





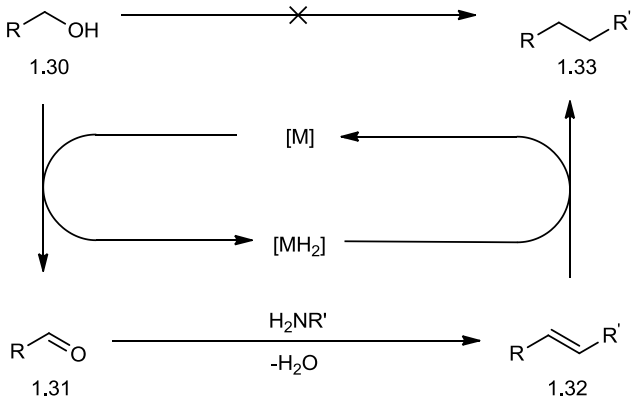
Scheme 1.27 *N-Alkylation of amines by ruthenium catalysts*

In 2010, Williams and co-workers reported that $[Cp^*IrI_2]_2$ is also an effective catalyst for the alkylation of amines with alcohols, with water used as the solvent in this reaction. Importantly, the reaction has no requirement for the addition of ligand or any base to activate the catalyst (Scheme 1.28).[45]



Scheme 1.28. *Borrowing hydrogen reaction using $[Cp^*IrI_2]_2$ catalyst*

There has been significant recent interest in the alkylation of amines with alcohol using hydrogen transfer catalysts as an alternative to conventional alkylation procedures. The *N*-alkylation of amines with an alcohol is a method for forming a carbon-nitrogen bond which involves the direct condensation between an amine and an alcohol. In this chemistry, the hydrogen transfer catalysts operate by an activation of the alcohol to an aldehyde in a process that we have termed "Borrowing Hydrogen Methodology". The borrowing hydrogen method typically uses ruthenium or iridium as the catalysts, removing hydrogen from alcohol **1.30** to form aldehyde **1.31**. This aldehyde then reacts with the amine to form an imine **1.32** and the hydrogen is given back to give a C-N bond in the product **1.33** (Scheme 1.29).[44, 46]

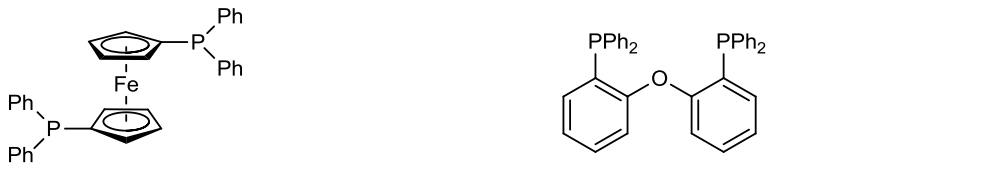


Scheme 1.29. *Borrowing hydrogen strategy in the alkylation of amines with alcohol.*

There are several advantages to use this method; (1) water is the only by-product avoiding the production of wasteful or toxic products, (2) alcohols are relatively inexpensive and more readily available than the corresponding halides or carbonyl compounds and the selectivity of the reaction can be controlled with the catalyst.

A catalytic system requires the efficient regeneration of the catalyst. The last step of this reaction is a hydrogenation process catalysed by the transition metal complex.[39] In hydrogenation processes catalysed by transition metal complexes, this is often accomplished through the addition of an oxidative or reductive agent for the generation of the desired product. The idea of "borrowing hydrogen" is that oxidation followed by reductive amination, presents a highly efficient and conceptually satisfying process with the additional benefit of possible implementations into the syntheses of natural products.[47]

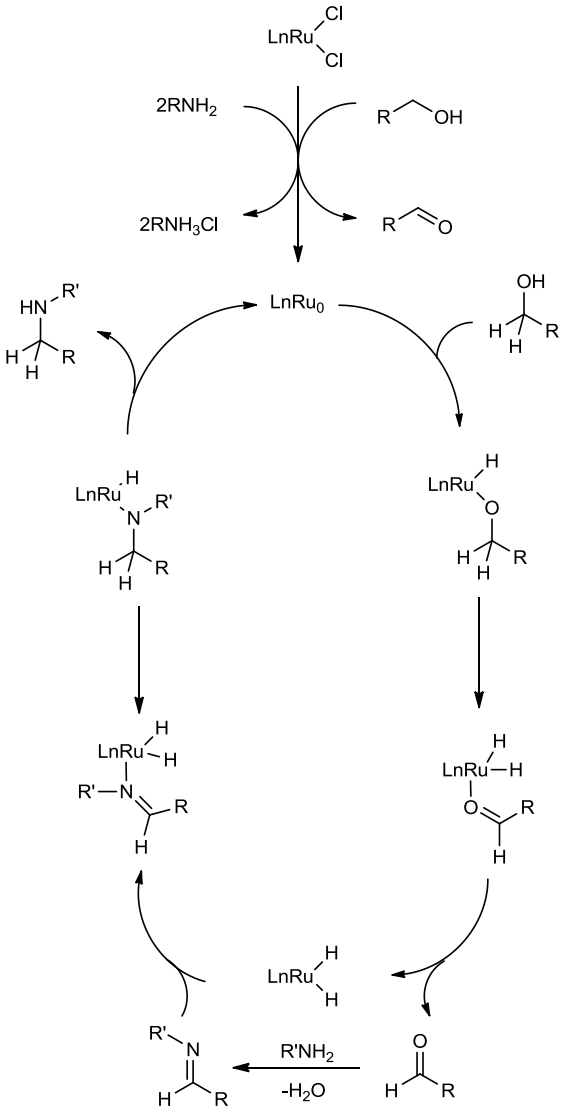
Transition metal complexes such as ruthenium or iridium can be used as catalysts with dppf or DPE-phos ligands for alkylation reactions (Figure 1.6).[48]



dppf = 1,1'Bis(diphenylphosphino)ferrocene DPEphos = (Oxydi-2,1-phenylene)bis(diphenylphosphine)

Figure 1.6. *Structures of dppf and DPEphos*

Reagents and complexes containing transition metals are important in modern organic synthesis because they allow otherwise impossible reactions to occur easily whilst also increasing the rate of chemical reactions.[49] The main transition group or d-block elements are essential materials to make ideal catalysts. A *d*-block metal ion has nine valence shell orbitals, in which to accommodate its valence electrons and with which to form hybrid molecular orbitals in bonding with other groups. The availability of these valence orbitals to the transition metal put it in the position of being able to form both σ- and π-bonds which is one of the key factors in imparting catalytic properties to the transition metals and their complexes.[50] Below is a mechanistic proposal for the *N*-alkylation of alcohols with amines using a Ru complex as the catalyst (Scheme 1.30).[41]



Scheme 1.30. *Mechanistic proposal for the N-alkylation of alcohols with amines*

Ruthenium complexes with phosphine ligands have proved successful catalysts for the *N*-alkylation of amines with alcohols.[48, 51] Transition metal ions can bind ligands to give a coordination compound or complex ML_n. The ability of transition-metal catalysts to accommodate both participative and non-participative ligands within their co-ordination sphere offers us the possibility of being able to direct the course of a reaction, between participative ligands by modifying the structural or electronic properties of the non-participative ligands. In this experiment, an advantage of phosphine ligands is the ability to individually and systematically alter the bonding

properties, electronic and steric effects of the ligands.[52]

1.5 Saccharides and Sensors

1.5.1 Saccharides

In biochemistry, saccharides are defined as a type of carbohydrate, an organic compound consisting only of carbon, hydrogen and oxygen. More accurately they are polyhydroxy-aldehydes and ketones. In nature, much biological saccharide chemistry is of paramount importance and saccharides are an important nutrient for the human body. Furthermore, ribose and deoxyribose are important materials for building nucleic acids.[53]

Carbohydrates can be divided into the following categories: monosaccharides, oligosaccharides and polysaccharides. Monosaccharides are the simplest, comprising of a single monomer carbohydrate, and are the basic unit to compose more complex carbohydrates. Most of monosaccharides have a sweet taste and are soluble in water, contain 3-7 carbon atoms and have the general formula $(C{\bullet}H_2O)_n$. According to the number of carbon atoms, monosaccharides can be defined as triose, pentose and hexose etc., the suffix *–ose* indicates a saccharide. Pentose and hexose are the most common types of carbohydrate, ribose and deoxyribose are pentoses, while glucose, fructose and galactose are hexoses.[54]

Those containing two units of monosaccharides are referred to as disaccharides. Disaccharides are formed *via* a dehydration reaction, one monosaccharide losing a hydrogen atom and the other a hydroxyl group. Maltose, lactose and sucrose are all examples of disaccharides. (Figure 1.7)

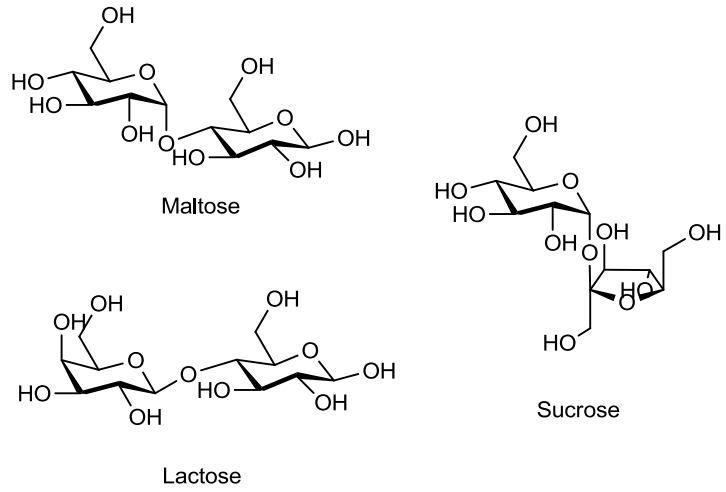


Figure 1.7. *Three type of disaccharides: maltose, lactose and sucrose*

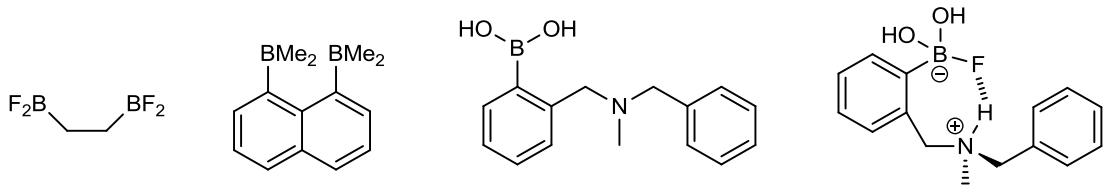
Longer chains of 3 to 10 monosaccharides bound together are commonly referred to as oligosaccharides, with examples such as maltose oligosaccharides, fructooligosaccharides, cyclodextrins and so on. They are difficult to break down by human digestive enzymes, so they are often used as low-calorie sweeteners and can promote the propagation of beneficial bacteria in the intestine. Polysaccharides are those containing more than ten monosaccharide units and monosaccharides or oligosaccharides can be generated by hydrolysis from polysaccharides.[55]

1.5.2 Sensors

Saccharides are ubiquitous in nature. They are involved in the metabolic pathways of living organisms, and in many medicinal and industrial applications, therefore it is very important to have sensors which can detect some saccharides. D-glucose is a biologically important saccharide and it is the source of energy for the living cell and metabolic intermediates. Glucose can be produced by plants through photosynthesis and it is easily absorbed into the blood. However, the breakdown of D-glucose transport in humans has been correlated with several diseases. For example, too

much D-glucose will increase the concentration of insulin, leading to obesity and diabetes, with too little causing hypoglycaemia or insulin shock. Recent health reports indicate that there is a strong relationship between obesity and many forms of cancer.[56]

Fluorescence is widely used in both the biochemical and pharmaceutical fields.[57] Through chemical reactions, fluorescent chemical groups can be attached to large biological molecules. Through the observed fluorescence of the attached group sensitive detection of these biological macromolecules is possible.[58] In 1967, Shriver and Biallas reported 1, 2-bis(difluoroboryl)ethane **1.34**, which has high affinity for the methoxide anion.[59] This changed the long-term concept that only metal ions can be used as anion receptors, so more fluorescent sensors for anion detection were developed such as compound **1.35**.[32b] Use of boronic acid fluorescent sensors for saccharide detection is a relatively new field. Czarnik published the first report in 1992[60] and D-Glucose selectivity was achieved two years later in 1994 by Shinkai and James.[61] The fluorescence of neutral boronic acid **1.36** can be quenched upon adding KF in 50% water-methanol buffer and the expected fluoride boronate **1.37** formed. James followed this research with enantioselective saccharide recognition in 1995.[62]



1.34 1.35 1.36 1.37

Figure 1.8. *Boronic acids as anion sensors.*

Therefore, the development of synthetic fluorescent boronic acid-based receptors and sensors for the detection of saccharides are an important proposal with potential applications such as enabling cancer to be detected at an early stage when it is more amenable to therapy.[56]

Boronic acids have been shown to form the corresponding boronic esters with 1,2- and 1,3-diols, such as those present in saccharides. Compounds containing two or more boronic acids have demonstrated selectivity of one saccharide over others depending on the spatial arrangement of the boronic acids and the manner of binding of the saccharide in relation to the size of the saccharide and the saccharide stereochemistry. Using a modular approach is a particularly effective way to develop new sensors for complex saccharides. The boronic acid sensors usually consist of three components: a receptor, a linker and a flurophore. (Figure 1.9)[56a]

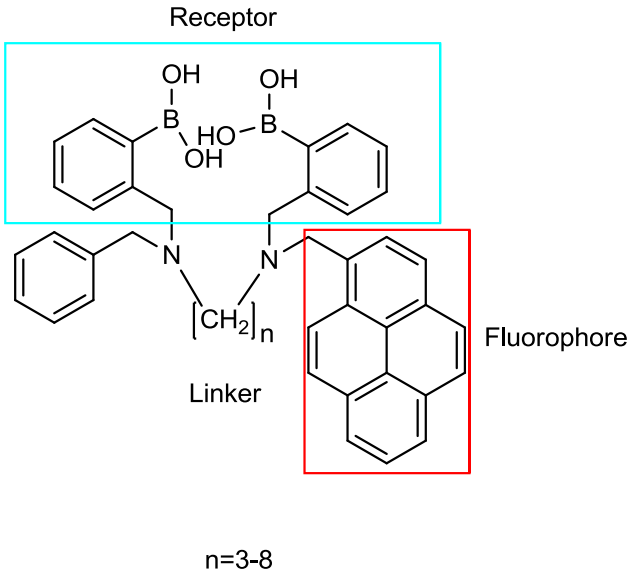


Figure 1.9. *Selective fluorescent sensor*

The fluorescent sensor has been shown to be selective for D-glucose when n=6. The length of linker has been shown to enhance selectivity for different saccharides. The pyrene fluorophore (read-out) unit has also been shown to tune saccharides selectivity.

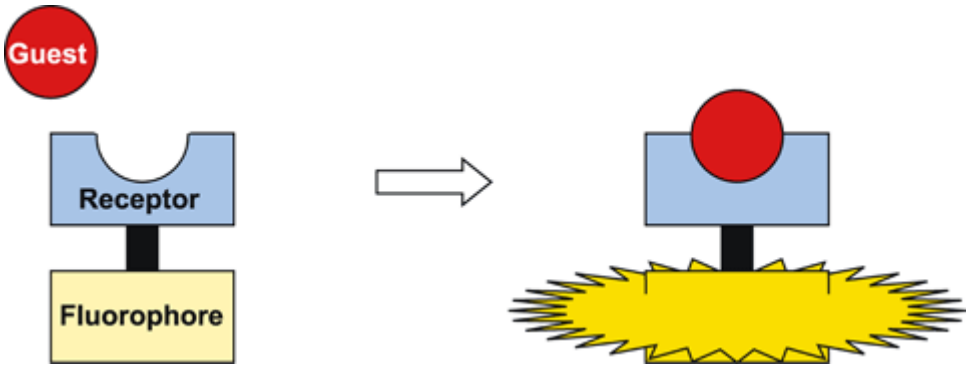
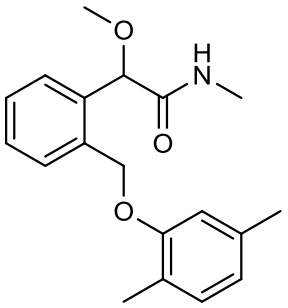


Figure 1.10. *Photoinduced electron transfer (PET) for a boronic acid fluorescence sensor*[56a]

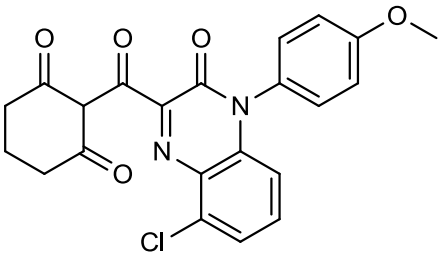
These fluorescent boronic acid-based sensors utilise an amine group proximal to boron, and the Lewis acid-Lewis base interaction between the boronic acid and the neighbouring tertiary amine plays a dual role. Firstly, the molecular recognition occurs at physiological pH. Secondly, communication of the binding event is observed by adjustment of the intensity of fluorescence emission through photoinduced electron transfer (PET).[60]

1.6 Introduction to Amides

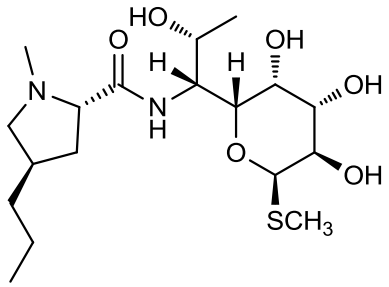
Amides can be seen as the products of carboxylic acids reacting with ammonia or amine compounds *via* condensation, and are one of the most important groups of compounds in chemistry. Amides are pervasive in pharmaceutical molecules, agrochemicals and natural products (Figure 1.11).



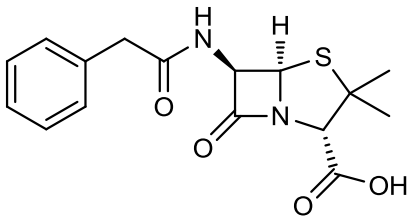
Mandestrobin 1.38



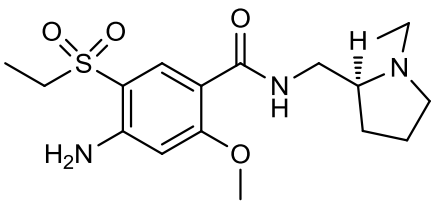
Fenquinotrione 1.39



Lincomycin 1.40



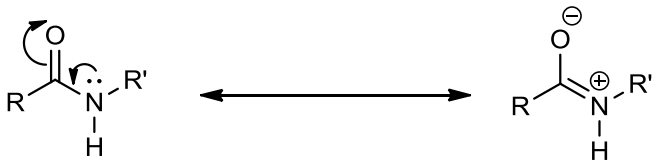
Penicillin 1.41



Amisulpride 1.42

Figure 1.11. *Amides in agrochemicals (1.38-1.39), drug molecules (1.40-1.42).*

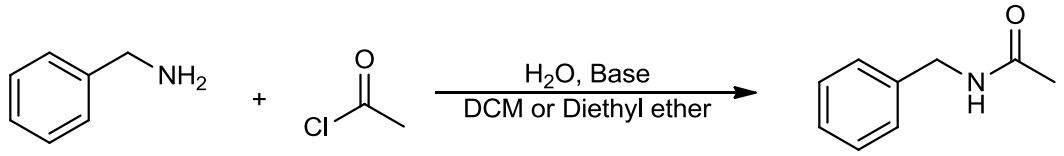
The C-N bond in amides is shorter than the C-N bond in amines, due to the sp^2 hybridised nature of carbon in the amide versus the sp^3 hybridisation of amine carbons. Additionally, the conjugation between the carbon and nitrogen in amides causes the C-N bond to have similar characteristics as double bonds. Most simple amides with a $RCONH_2$ structure are colourless solids except methanamide. Amides have good stability and they are very difficult to hydrolyse. Moreover, amides are weakly alkaline and can react with acids to form the corresponding salt. The lone pair of electrons on the nitrogen can be delocalised into the carbonyl and form a partial double bond between the carbonyl carbon and nitrogen (Scheme 1.31).[61]



Scheme 1.31. *Resonance of amides.*

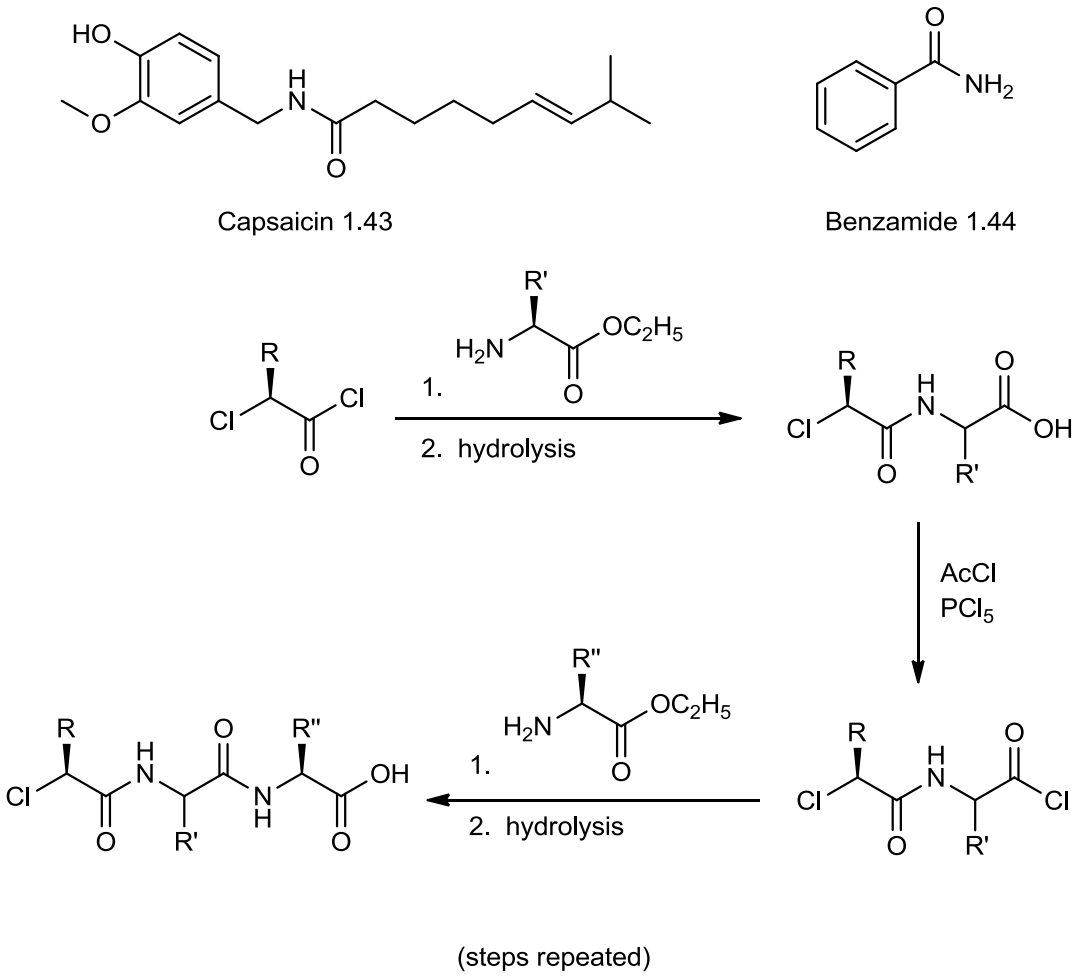
1.6.1 Amide Formation

In 1883, the popular method for synthesising amides from amines and acid chlorides was described by German chemists Carl Schotten and Eugen Baumann. In this reaction an acid chloride reacts with an amine to form an amide, with addition of base in order for the reaction to proceed, due to the formation of an acid by-product. An aqueous solution of base needs to be added slowly to the reaction mixture in order to neutralise the acid and stop the amine salt from forming. A two-phase solvent system consisting of water and an organic solvent such as DCM is usually used in this reaction. The product and any remaining starting material remain in the organic phase, while the acid is neutralised by base within the water phase.[62-63]



Scheme 1.32. *The Schotten-Baumann reaction.*

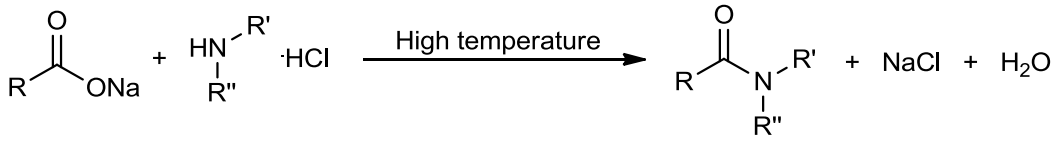
The Schotten-Baumann reaction is widely used in organic chemistry. Prominent examples include the synthesis of capsaicin **1.43**, the synthesis of benzamide **1.44** from benzoyl chloride and a phenethylamine and Fischer peptide synthesis (Scheme 1.33).[64]



Scheme 1.33. *Capsaicin, benzamide and Fischer peptide synthesis.*

The Fischer Peptide synthesis results in the formation of a polypeptide. α-Chloro or α-bromo acyl chloride is treated with an amino acid ester, followed by hydrolysis of the resultant ester into the acid and then conversion into a new acid chloride. The product can then condense with a second amino acid ester, repeating the process. The terminal chloride is finally converted into an amino group with ammonia.

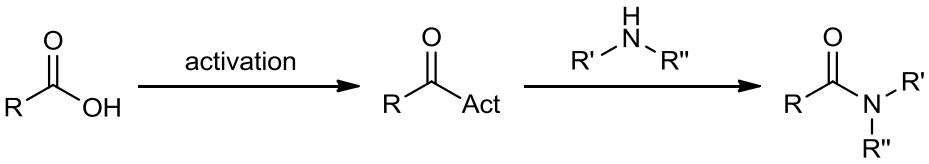
The direct uncatalysed formation of amides usually requires high temperatures and the first report of which was published in 1902 by Dunlap. Using the sodium salts of carboxylic acids and amine hydrochloride salts as reagents and the reaction was run under very high temperatures. All amide products were purified and isolated yields were between 23% and 72% (Scheme 1.34).[65]



Scheme 1.34. *Formation of amides from carboxylic acid sodium salts and amine hydrochloride salts.*

In recent years, Cossy, Whiting and GöoBen reported similar methods to synthesise a range of amides at high temperature in the presence of molecular sieves.[66]

Using coupling reagents in amide bond formation is very important in organic synthesis. Amide bonds are usually synthesised from carboxylic acids and amines, but the unification of both of them does not occur spontaneously at ambient temperature. Amides can only be produced using high temperature and without any water.[67] For this reason, the carboxylic acid needs to be activated, with the –OH group of the acid being converted into a good leaving group prior to treatment with the amine (Scheme 1.35).[68]

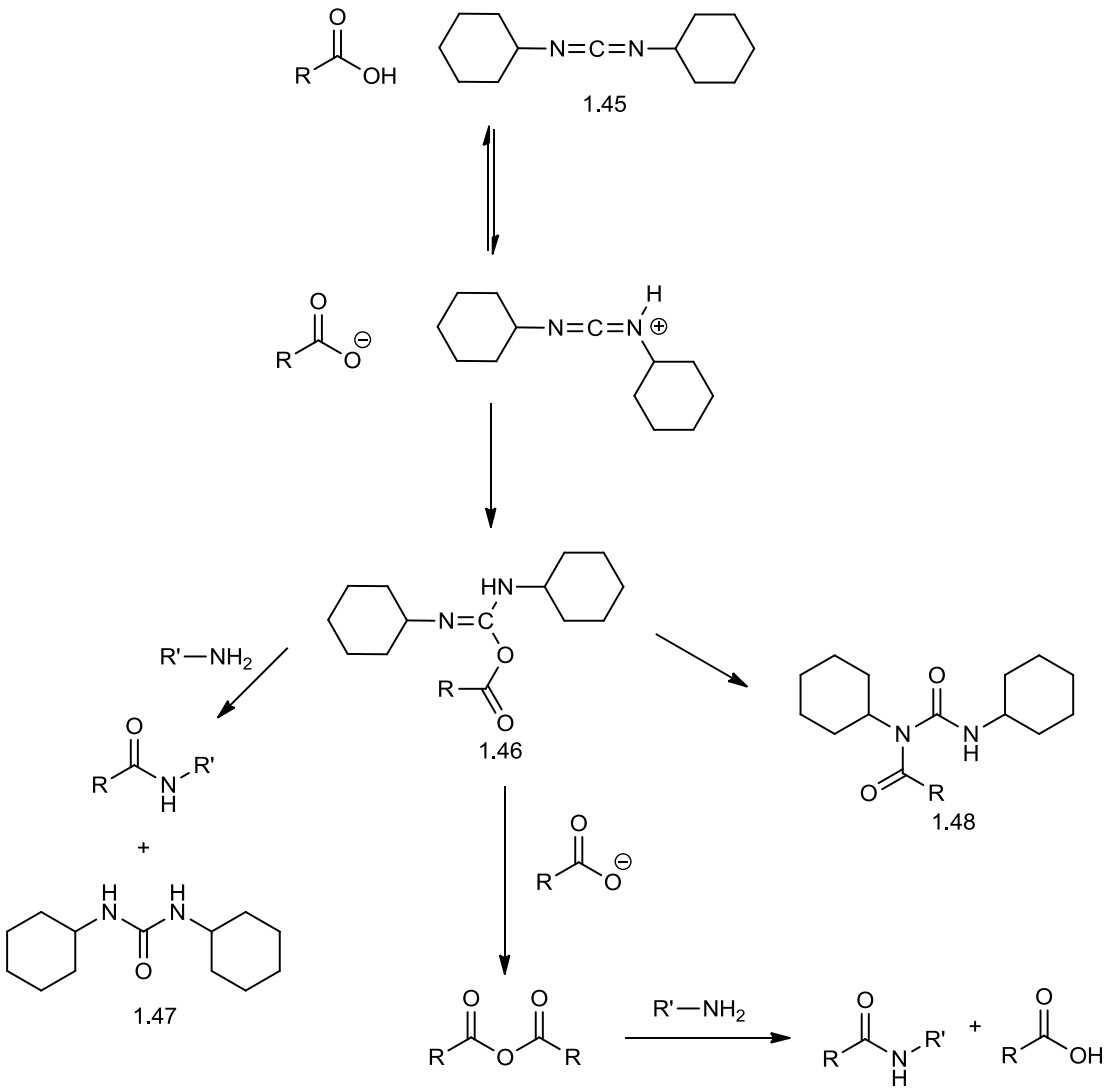


Scheme 1.35. *Principle of the activation process for amide-bond formation.*

Reported in 1955, dicyclohexylcarbodiimide (DCC, **1.45**) was used for coupling carboxylic acids to amines which is shown in Scheme 1.36.[69]

In the first step, the carboxylic acid reacts with DCC to from the *o*-acylurea **1.46**, and then this intermediate can go on to yield several different products:

1. Side-product DCU **1.47** will be formed when the amide is directly coupling with the amine, but it can be removed easily as it is usually insoluble in the reaction solvent.
2. 2 equivalents of acid and *o*-acylurea react with another molecule of carboxylic acid giving a carbonic anhydride, which can subsequently yield the amide by reaction with the amine.
3. Acyl transfer from O to N, giving the by-product *N*-acylurea **1.48**.



Scheme 1.36. *Amide formation using DCC as coupling reagent.*

Since the application of DCC, many other carbodiimide derivatives (such as **1.49**, **1.50**) have been reported that were also good for amide bond formation.[70] However, the disadvantage of using DCC and DIC is that they are very difficult to remove them after the reaction finishes. Tertiary and quaternary amine carbodiimides (**1.51**-**1.55**) have been reported by Sheehan. He concluded that tertiary amine carbodiimide mediated couplings were more efficient than quaternary derivatives. More carbodiimide derivatives were developed and reported later (**1.56**-**1.58**).[71]

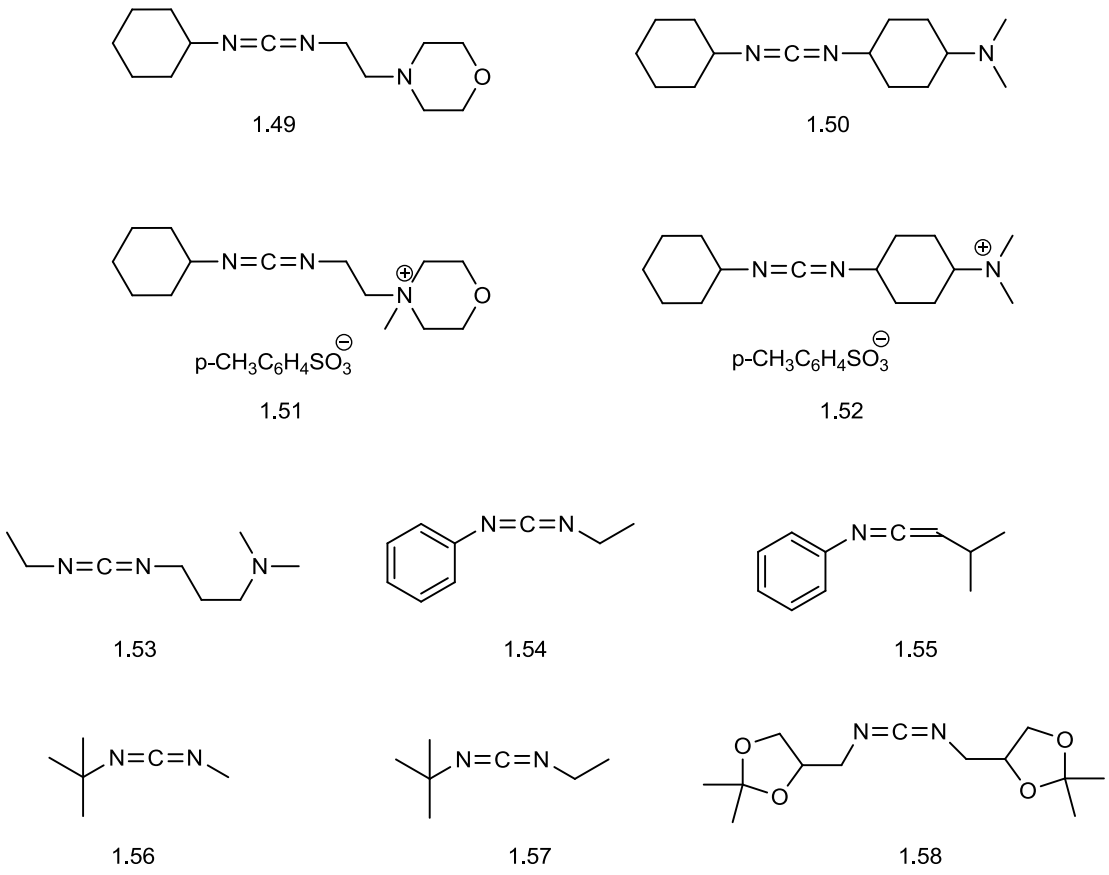
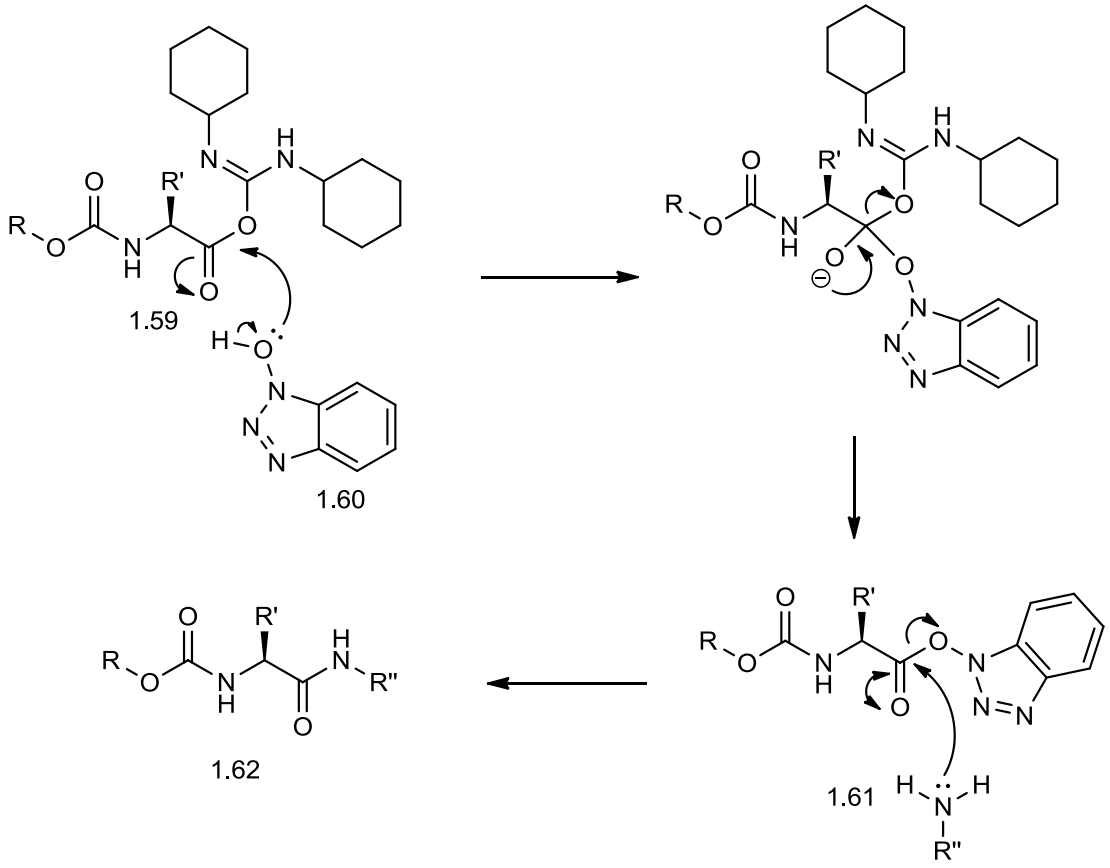


Figure 1.11. *Structures of some more carbodiimides.*

In 1970, Koenig and Geiger developed the additive HOBt **1.60** (1-hydroxy-1 *H*-benzotriazole) to reduce the level of epimerisation when using carbodiimides as coupling reagents, successfully coupling Z-Gly-Phe-OH to H-Val-OMe.[72] The generally accepted mechanism is shown in Scheme 32. This successfully increased the yield and the epimerisation levels were reduced from 35% to 1.5%. HOBt **1.60** first reacts with *o*-acylurea **1.59** to form the active ester **1.61**, which further reacts with an amine to form the final amide product **1.62**.[70]



Scheme 1.37. *Amide formation using 1-hydroxy-1 H-benzotriazole as an additive with DCC*

There are more additive salts coupling reagents based on 1*H*-benzotriazoles, such as uronium **1.63**, aminium **1.64**, phosphonium **1.65** and immonium **1.66**, all of which improve the activation of the carbodiimide couplings.[73]

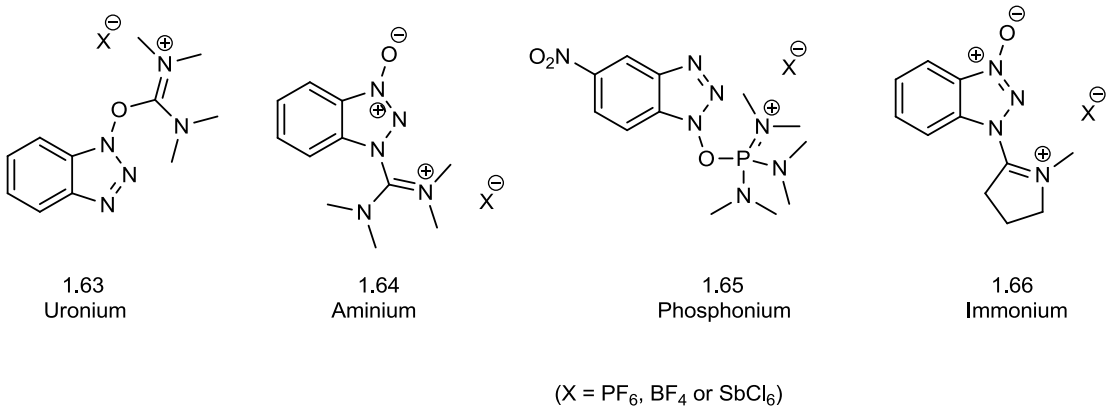
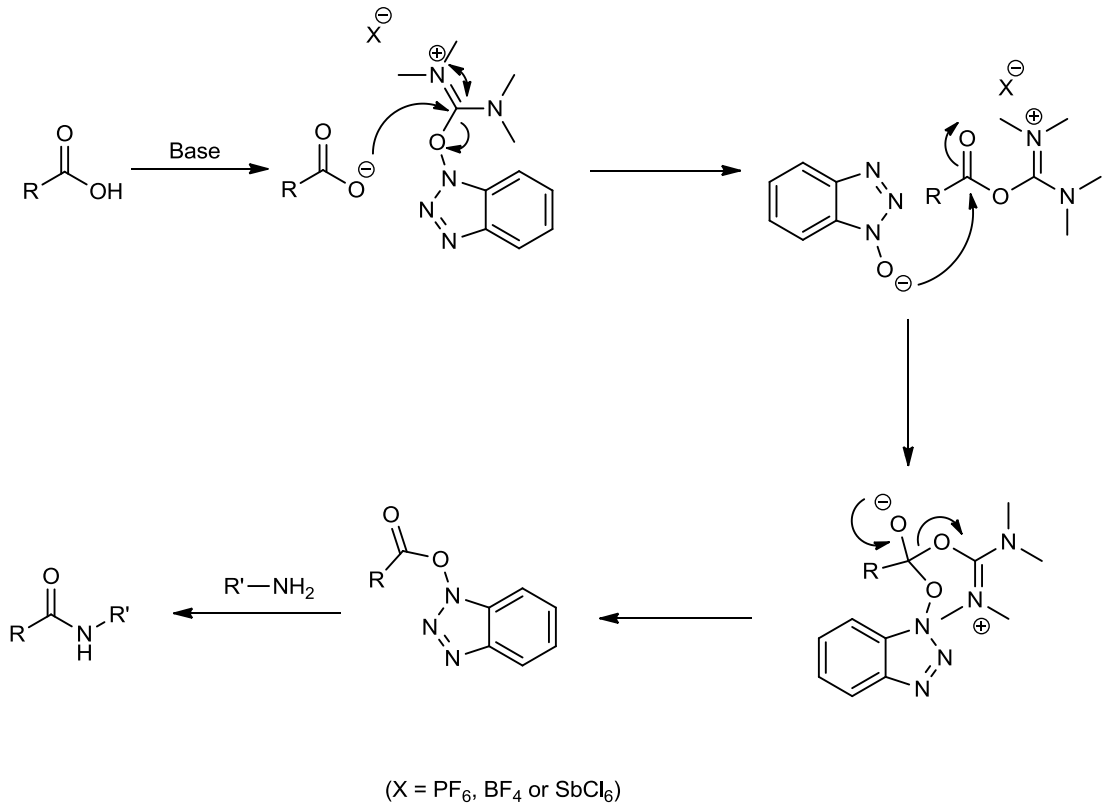
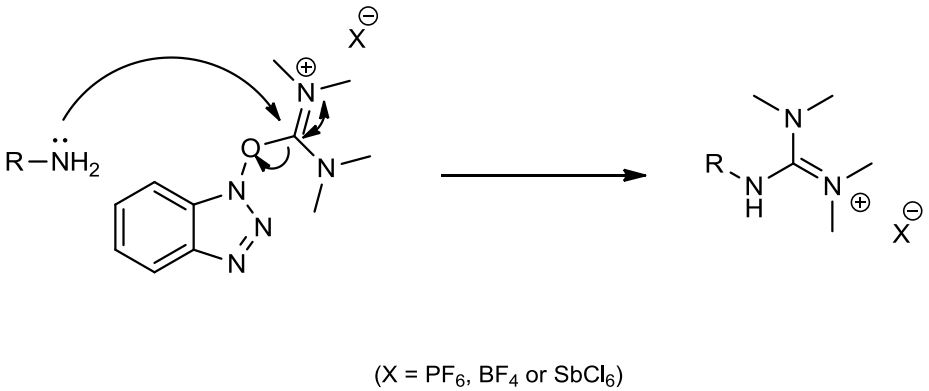


Figure 1.12. *Coupling reagents based on 1H-benzotriazole*

Uronium and aminium isomers of these reagents can react with carboxylic acids to form OAt/OBt active esters, which can further react with amines to form the final amide (Scheme 1.38). The by-product guanidinium is often produced when the amine reacts with the coupling reagent (Scheme 1.39).[73d]



Scheme 1.38. *Using uronium/aminium reagents for amide formation.*



Scheme 1.39. *Guanidinium formation.*

The first synthesis of a dipeptide using acid chlorides for coupling was reported by Fischer in 1901. The general method includes the use of reagents such as thionyl chloride or phosphorus pentachloride to activate the carboxylic acid which reacts with amines to form amides swiftly.[74] However, the conditions of this method are very harsh, and many reagents have been developed to avoid this. Some examples are shown in Figure 1.13.[75]

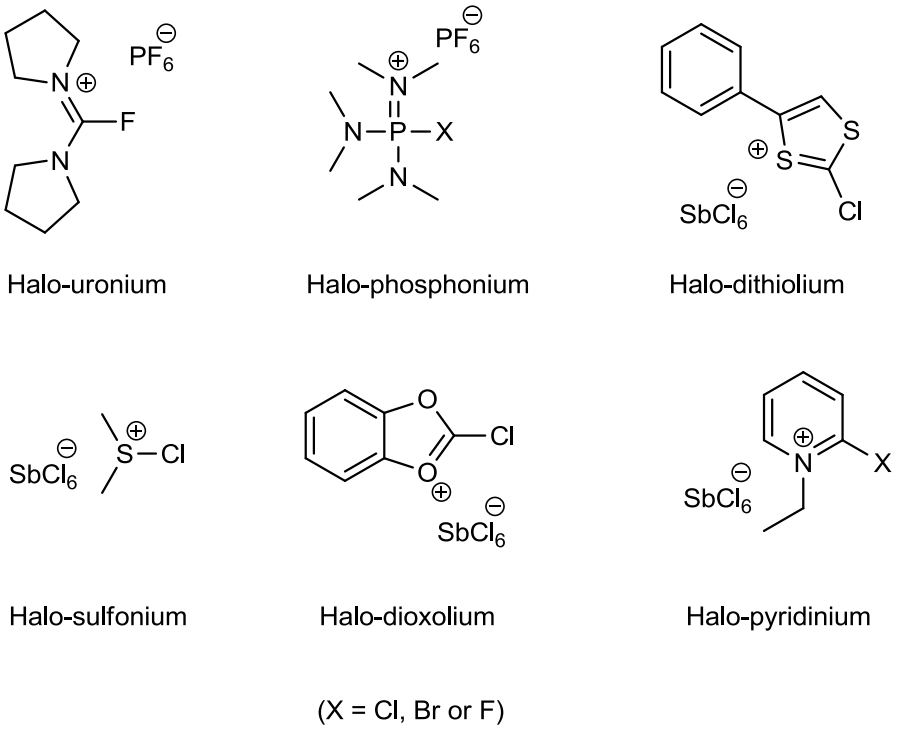


Figure 1.13. *Acid halide generating coupling reagents.*

There are many other classes of coupling reagents which have been developed, including triazine-based reagent **1.67**,[76] Pentafluorophenol (HIPfp)-based reagent **1.68**,[77] 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HODhbt)-based reagent **1.69**,[72a] 2-hydroxysuccinimide (HOSu)-based reagent **1.70**,[78] 2-(5-norbornene-2,3-dicarboximide) (HONB)-based reagent **1.71**,[79] Phosphorus-type (PyTOP)-based reagent **1.72** and miscellaneous reagent **1.73** (Figure 1.14).[80]

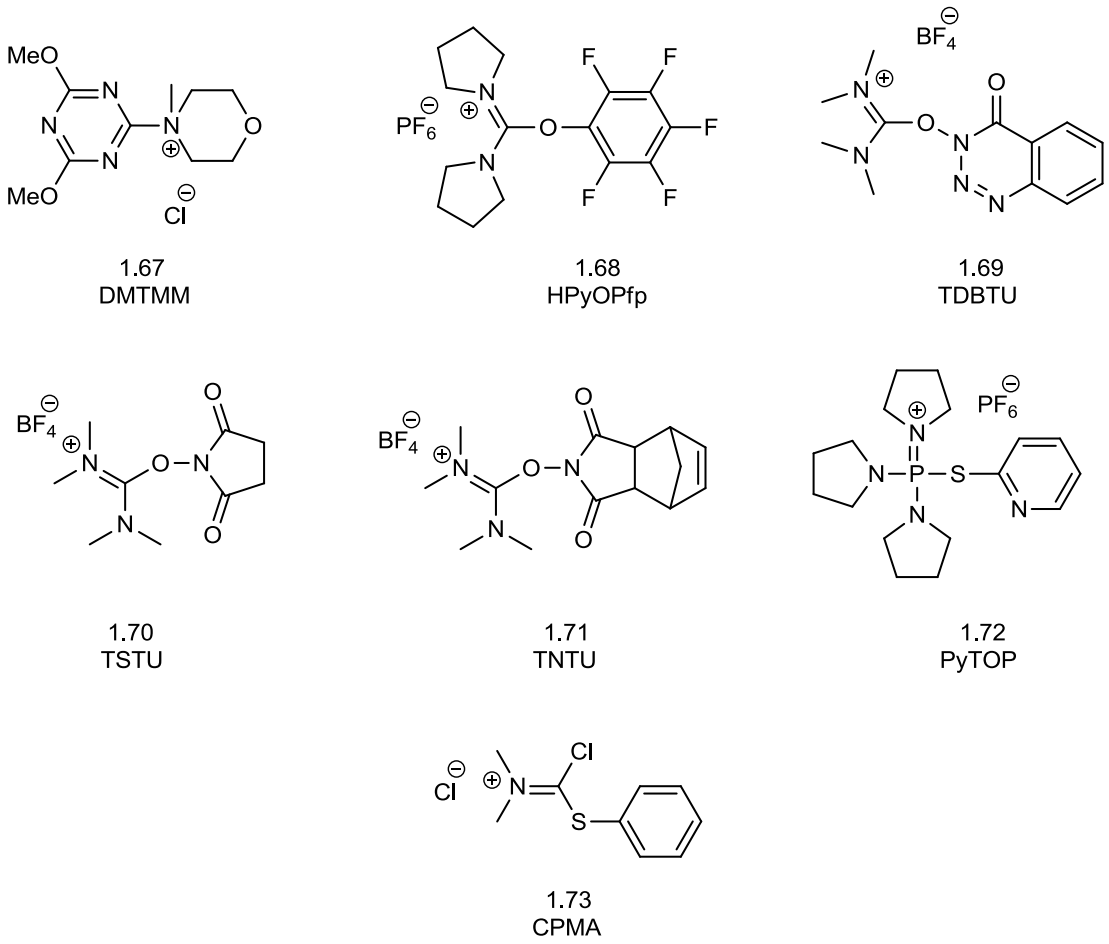
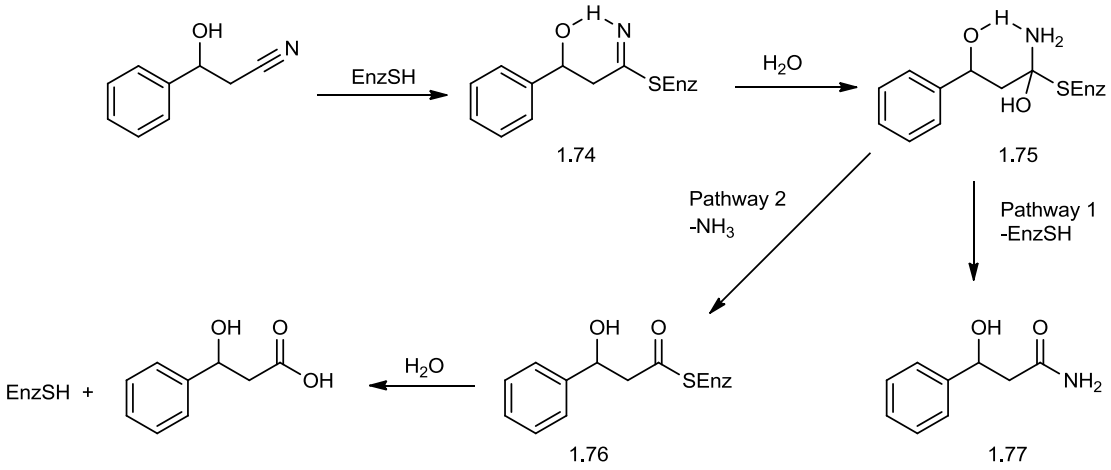


Figure 1.14. *Other classes of coupling reagents.*

Although lots of coupling reagents have been reported, none of them are efficient for a broad range of amide bond formation. Some reagents are better than others in certain areas, such as producing limited by-products, a short reaction time, low-levels of epimerisation and high conversions. Finding a universal coupling reagent is an area still to be developed.

Enzymatic methods have proved successful in some amide bond formations and have been used in laboratories and in industry for the synthesis of drug molecules, natural products and bioactive peptides. In 2006, an example of primary amide formation was reported by Mukherjee and co-workers. They used several different β-hydroxynitriles and converted them into the corresponding amides by using

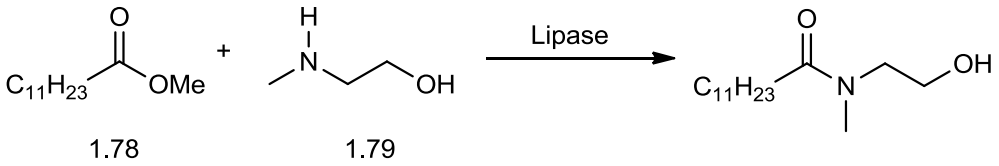
nitrilase $ZmNIT_2$ which was isolated from maize.[81]



Scheme 1.40. *Amide formation in $ZmNIT_2$-catalyzed hydrolysis of β-hydroxy nitriles.*

It is possible that the lone pair of electrons on the nitrogen atom can form a hydrogen bond with the β-OH group in the enzyme substrate complex **1.74**. The tetrahedral intermediate **1.75** could be generated by adding H_2O and there are two pathways to form different products. Pathway 1 involves breaking the C-S bond to yield amide **1.77** pathway 2 looses ammonia to form intermediate **1.76** which is then further hydrolysed to yield a carboxylic acid. However, pathway 1 is more favourable than pathway 2 as much more energy is required to break down the six-membered ring and release the ammonia. Therefore, primary amides are the major products in this reaction.

Efficient selective synthesis of the secondary amide from methyl laurate **1.78** and *N*-methylethanol amine **1.79** by using different lipases was demonstrated in 2005 by Sharma.[82] They found that acetonitrile was the best solvent for these kinds of reactions. The molar ratio of the reactants and the reaction temperature could strongly influence the rate of the reaction.



1.78 1.79

Scheme 1.41. *Enzymatic amidation in acetonitrile*

Although there are many other successful methods for using enzymes for amide bond formation, most of these methods are still limited. Therefore, there is much work needed to find the best reaction conditions for enzymatic amide bond formation.

The first highly active boronic acid catalyst for amide synthesis was reported by Yamamoto and co-workers in 1996.[83] They reported that just 1% of 3,4,5-trifluorobenzeneboronic acid **1.80** or 3,5-bis(trifluoromethyl)benzene-boronic acid **1.81** as the catalyst was needed for successful amidation between carboxylic acids and amines. All reactions had to be run in anhydrous toluene, xylene or mesitylene with molecular sieves at temperatures between 110 – 150 °C for about 18 hours, achieving a range of secondary and tertiary amides in good yield (scheme 1.42).

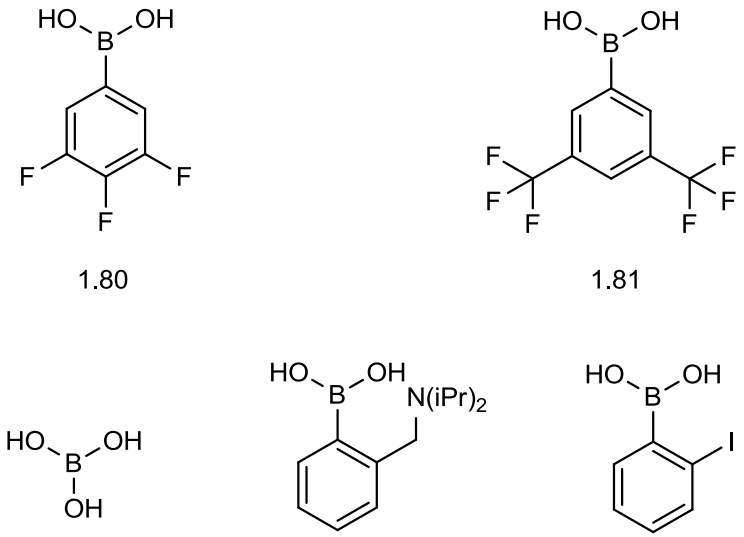
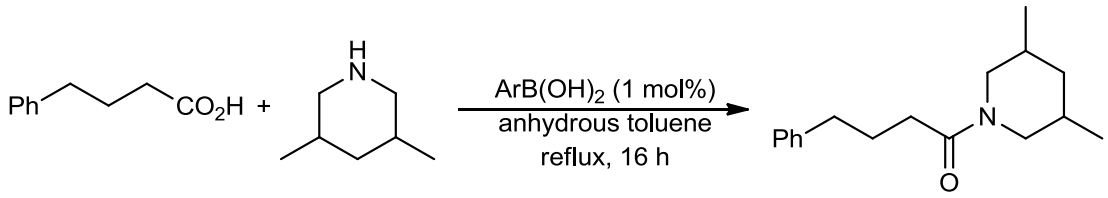
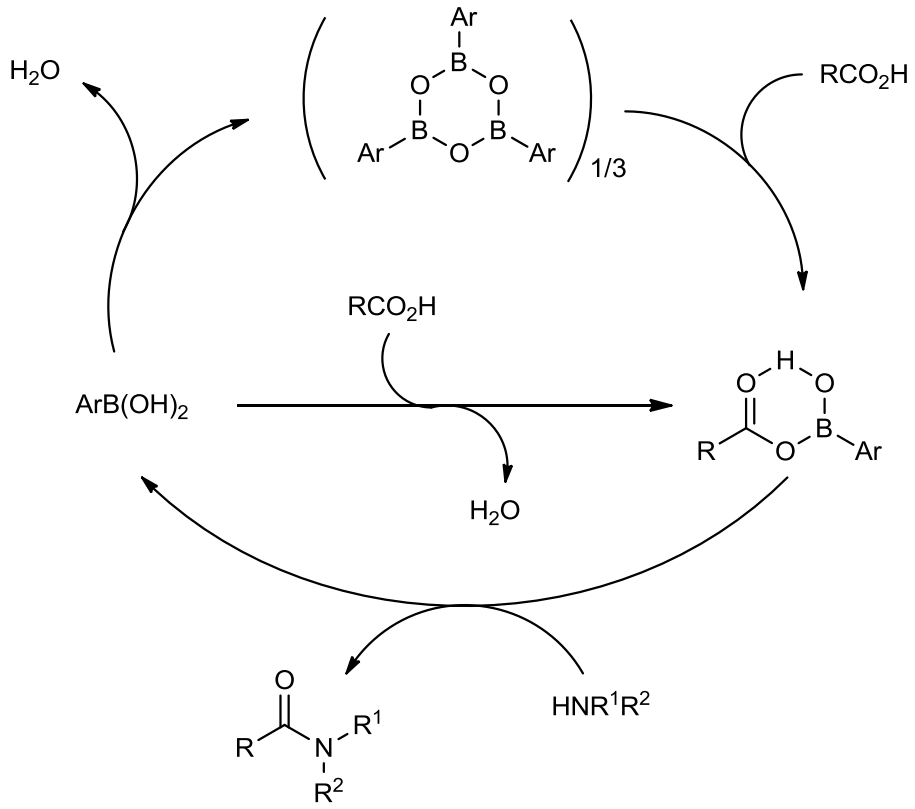


Figure 1.15. *Boronic acid catalysts.*



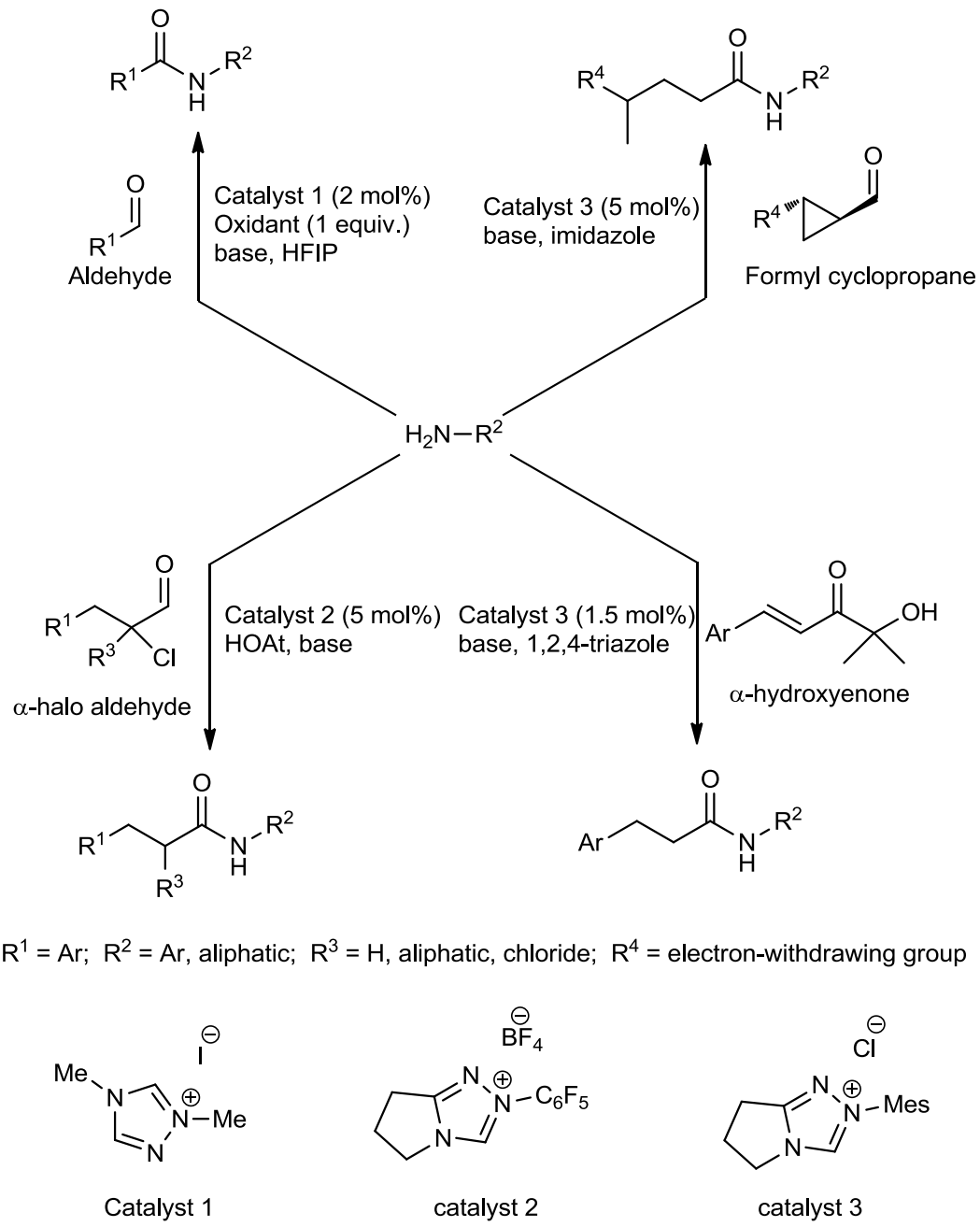
Scheme 1.42. *An example of an amidation reaction catalysed by arylboronic acids.*

The mechanism proposed as shown below explains the reactivity of boronic acids in this reaction (Scheme 1.43). Arylboronic acids usually contain varying amounts of cyclic trimeric anhydrides (boroxines). The mono-(acyloxy)boronic acid could be produced by mixing 2 equivalents of 4-phenylbutyric acid with 1 equivalent of arylboronic acid in toluene. If 1 equivalent of benzylamine is directly added to mono-(acyloxy)boronic acid at room temperature without removal of water, then the yield of the corresponding amide would be less than 50% due to mono-(acyloxy)boronic acid decomposing upon hydrolysis with water. Therefore molecular sieves are necessary for these reactions.



Scheme 1.43. *Proposed mechanism of boronic acid catalysed amide bond formation.*

N-Heterocyclic carbene (HNC) catalysts and co-catalysts can also be used to generate activated carboxylate that react with a variety of amines, forming the corresponding amides.[84] These reactions require only catalytic amounts of reagents and create a promising solution to avoiding by-product generation in traditional amide formations.

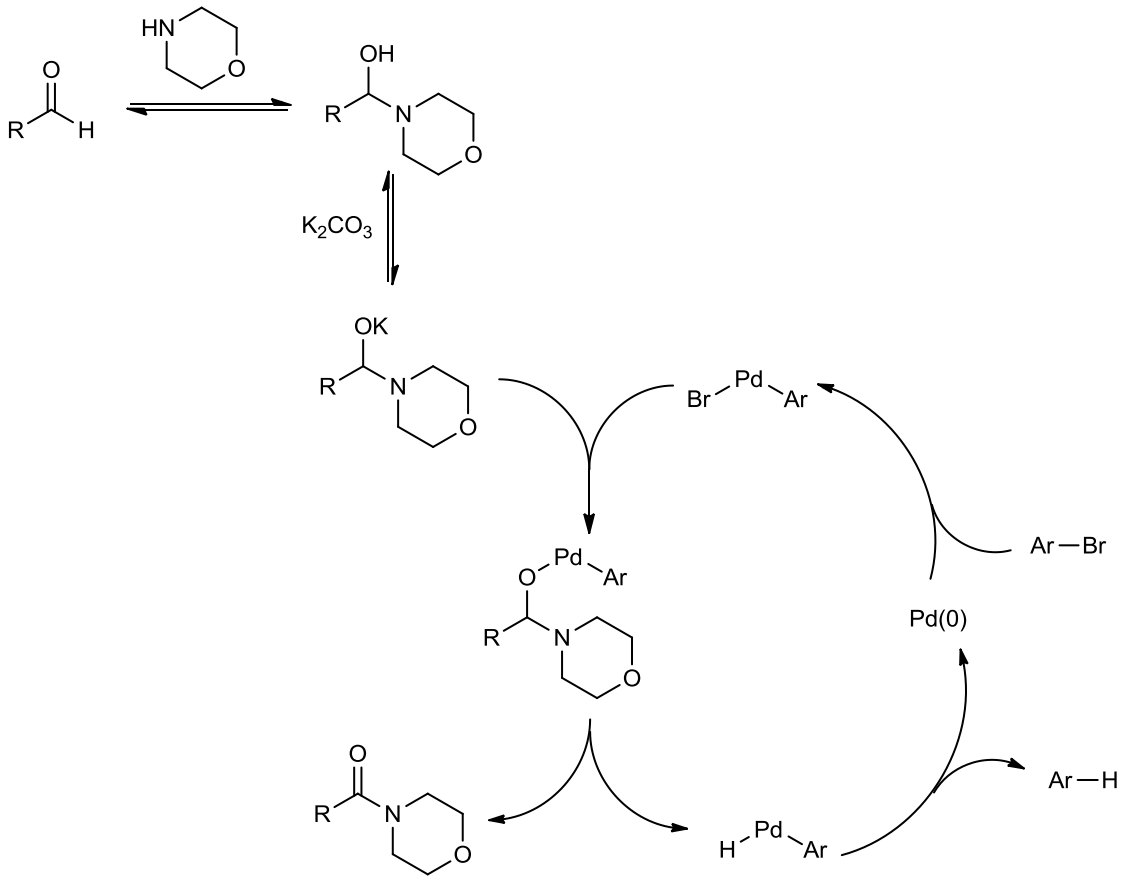


Scheme 1.44. *Organocatalytic redox and oxidative amidation.*

In a recent industry-led survey of 128 drug syntheses, acylations accounted for 12% of the reactions involved, just less than heteroatom alkylations/arylations. Roughly 66% of them used *N*-acylations to form amides. However, none of these *N*-acylation reactions were catalytic, although they accounted for a large proportion of conversion. Therefore, the development of some environmentally friendly catalytic

processes to synthesise amides is necessary.

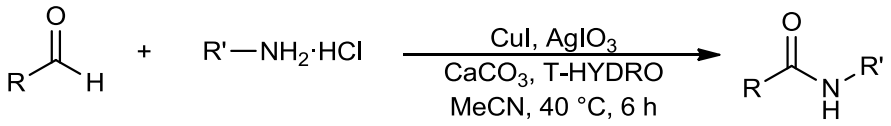
Several metal catalysts and oxidants have been reported for amide formation from simple aldehydes or alcohols. The first transition metal catalysed amidation of an aldehyde to the corresponding amide was reported by Tamaru and co-workers in 1983. They used the palladium catalysed oxidative transformation of aldehydes to amides and a possible catalytic cycle is shown in Scheme 1.45. The alkoxypalladium reagents were key intermediates which could be decomposed to provide the corresponding amide and hydridopalladium.[85]



Scheme 1.45. *Palladium catalytic cycle for the oxidative transformation of aldehydes to amides.*

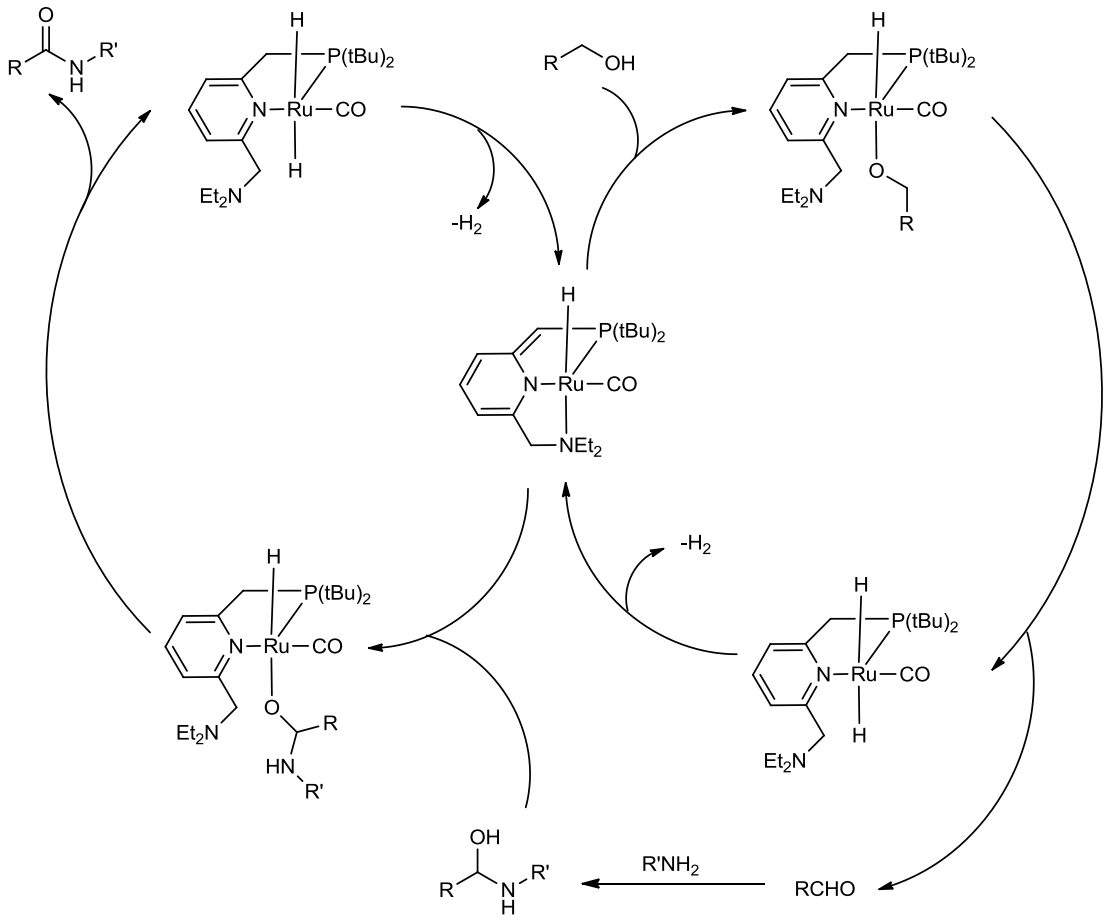
In 2006, Yoo and co-workers developed an efficient copper/silver-catalyst for the

formation of amide from aldehydes and amine hydrochloride salts with tert-butyl hydroperoxide (TBTH) as an oxidant. However, yields were decreased when they used aliphatic or electron-poor arylaldehydes.[86]



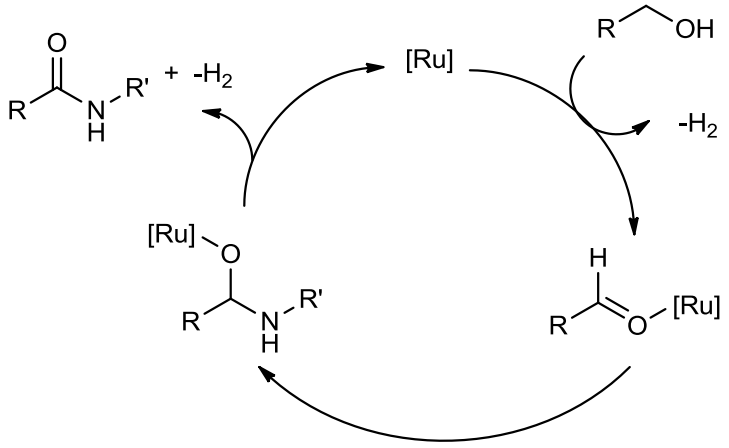
Scheme 1.46. *Copper-catalysed oxidative amidation of aldehydes with amine hydrochloride salts.*

Several important examples of using ruthenium catalysts for formation of amides from alcohols and amines were developed. In general, these kinds of reactions proceed in a clean atom-economical mode without any additives, acid or base, and usually the only side-product was hydrogen. In 2007, Milstein reported the first amide formation reaction catalysed by a ruthenium pincer complex. In this reaction, amines were directly reacted with same amounts of alcohols to produce the amide in high yield and hydrogen gas was the only by-product. The catalytic cycle for Milstein's catalyst is shown in Scheme 1.47.[87]



Scheme 1.47. *Proposed mechanism for the direct acylation of amines by alcohols catalysed by ruthenium catalysts*

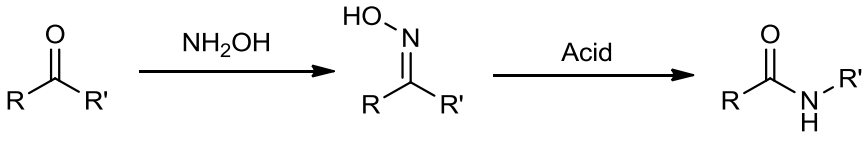
In 2008, the group of Madsen reported a new catalyst system for the direct synthesis of amides from alcohols and amines by the extrusion of dihydrogen (Scheme 1.48).[88]



Scheme 1.48. *Ruthenium-catalyzed amide formation*

Although there are many other ruthenium catalysts which have been identified for this amide formation, there was no real improvement in terms of yield or scope of reagents over Milstein's ruthenium catalyst.

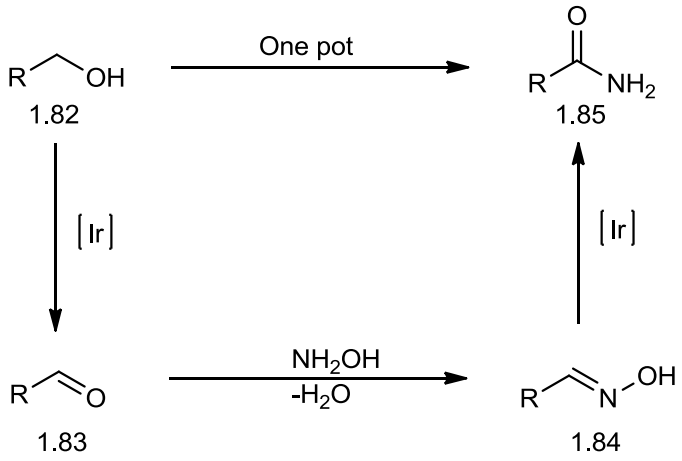
Oximes have been used in amide bond synthesis for long time, for example in the Beckmann rearrangement of ketoximes and aldoximes into amides. The Beckmann rearrangement is a traditional method to form an amide, but high temperatures and strong acids are required. The reaction starting with ketones reacted with hydroxylamine to form an oxime as the intermediate, and then connection to the corresponding amide by treating with acid.[89]



Scheme 1.49. *Beckmann rearrangement*.

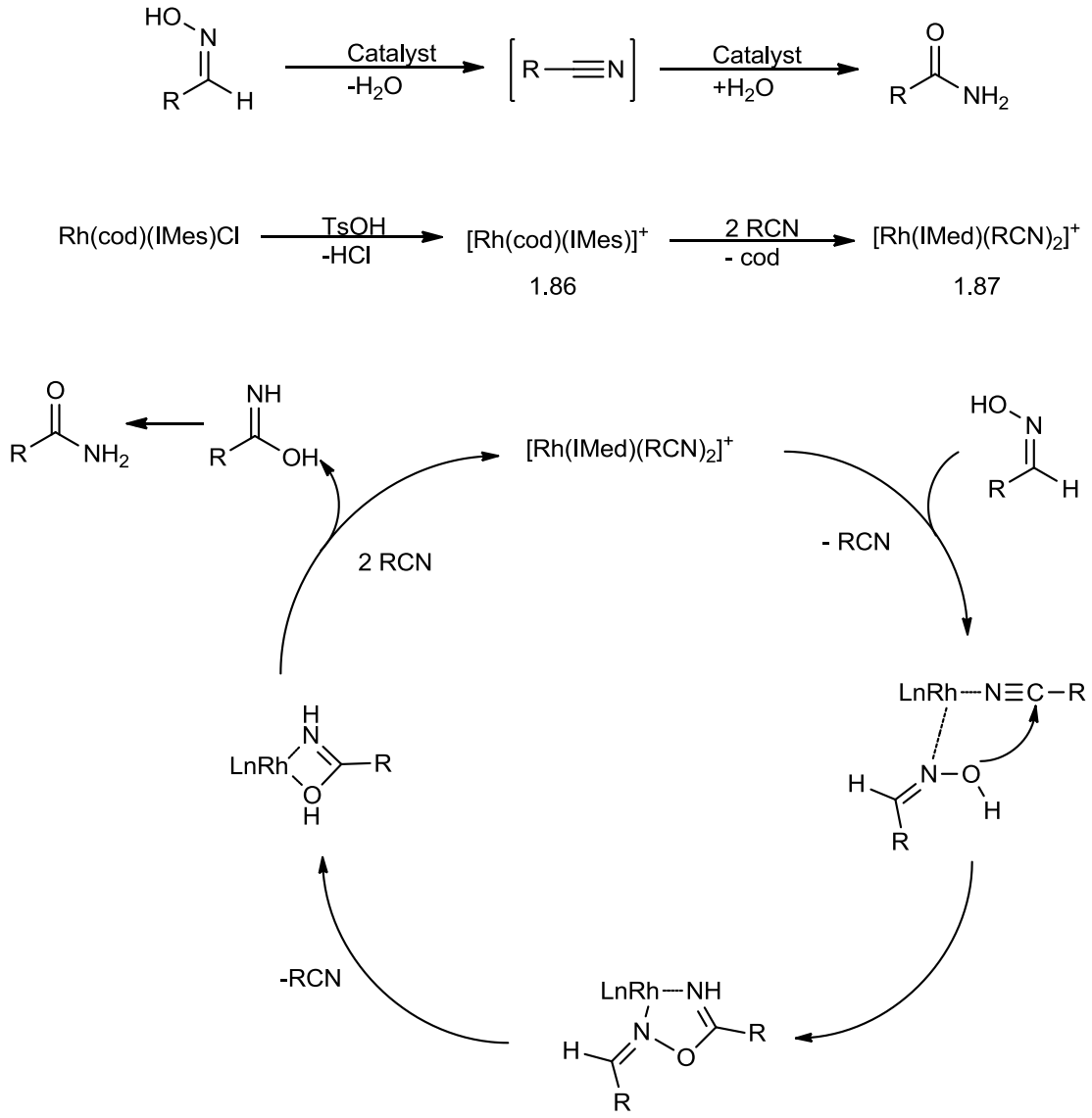
Chang and co-worker reported the first catalytic conditions for rearrangement of aldoximes into primary amides starting from an aldehyde in 2003 using Wilkinson's complex.[90] Afterwards, more metal-based catalysts have been reported to be useful

for this rearrangement, such as iridium, ruthenium and palladium. A report by Williams demonstrates that the iridium catalyst $[Ir(Cp^*)Cl_2]_2$ is effective for the rearrangement of oxime to amide. The aldehyde **1.83** was oxidized from alcohol **1.82** by using the iridium catalyst and hydroxylamine hydrochloride was added to form the oxime **1.84**, and then the reaction undergoes the rearrangement to form the corresponding amide **1.85**.[91]



Scheme 1.50. *Converting alcohols into amides.*

In 2009, Chang and co-workers found the (cyclooctadiene)rhodium chloride-carbene complex (Rh(cod)(IMes)Cl) with *p*-toluenesulfonic acid and the corresponding nitrile additive was active towards the synthesis of a range of amides from aldoximes. A clear rate enhancement is seen in the presence of the nitrile; dehydration of aldoximes to nitriles was assumed to happen first followed by hydration of the nitrile intermediates. The neutral rhodium complex is changed to its cationic species **1.86** by Brønsted acid, and then a cod ligand is released when the nitrile intermediates binds with the cationic complex **1.86** giving species **1.87**.[92]



Scheme 1.51. *Nitrile-mediated mechanistic proposal of the Rh-catalysed aldoxime conversion.*

1.7 Summary

Since 1860 the first isolation of a boronic acid has been reported by Frankland, boronic acids started to become very useful building blocks for organic synthesis. There are many cross-coupling reactions by using a palladium catalyst and boronic

acid with a halide or triflate to form new C-C bond. There are many publications focused on boronic acid when the first boronic acid drug was synthesised.

Amines are an important class of compound in bulk chemistry and also present as important intermediates in organic synthesis. There are various methods of synthesising amines, such as Hofmann degradation, Buchwald-Hartwig reaction and *N*-alkylation of alcohol.

There are a large number of studies focused on nitrogen-boron bonding. The energy of the amine – boronic acid (N-B) interaction in a boronic acid has been calculated by potentiometric titration to be in the range of 15 to 25 kJ mol^{-1}.

The direct alcohol with *N*-alkylation of amines is an environmentally friendly and more atom-efficient method in the synthesis of amines, because during this transformation it produces water as the only by-product.

The primary interaction of a boronic acid with a diol is covalent and involves the rapid and reversible formation of a cyclic boronate ester. Therefore, fluorescent boronic acid-based receptors and sensors are ideally suited to the recognition of saccharides.

In 1883, the popular methods for uncatalysed coupling of amines and acid chlorides have become well known reactions for the construction of amide bonds. The use of coupling reagents to activate a carboxylic acid towards nucleophilic attack by an amine is the most common direct coupling reaction method of amide bond synthesis. However, catalytic amide bond syntheses have opened up new routes to amide bond formation.

2. Results and Discussion Ⅰ – Borrowing Hydrogen

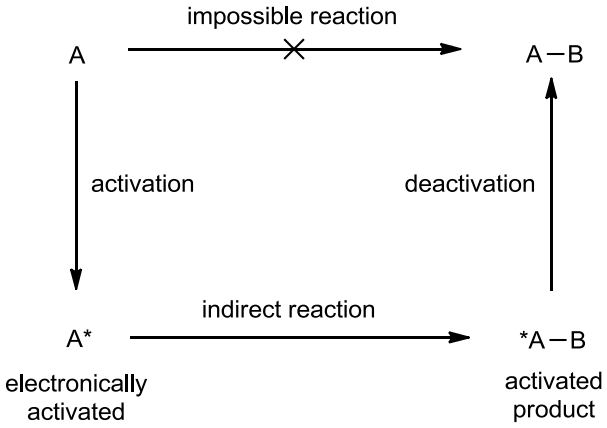
2.1 Aims

The research discussed in this thesis has investigated the use of alcohols as alkylating agents for the formation of new C-N bonds. Alcohols are generally cheaper, more stable and less toxic than conventional alkylating agents such as alkyl halides. At the heart of this chemistry is the temporary activation of an alcohol to a carbonyl compound by a process that the Williams group has termed “borrowing hydrogen”. The conversion of a primary amine into a secondary amine and a secondary amine into tertiary amine by alkylation with an alcohol is a known reaction which the Williams group has further developed with iridium catalysts along with some more active ruthenium catalysts. The only by-product formed during these reactions is water.

This strategy will be applied to the synthesis of a range of new boronic acid amine compounds first, and then will be further applied to the synthesis of a range of boronic acid molecular sensors (discussed in Chapter 3), providing an alternative to the traditional methods which use mutagenic alkyl halides as the alkylating agents. As the project develops, more complex structures may be prepared and the coupling process will allow rapid access, hopefully under equilibrium control where the sugar acts as a template for the construction of the sensor. More boronic acid sensors can be made by this “borrowing hydrogen” methodogy which can be used in medical applications for the diagnosis of diabetes or the detection of pathogens and cancer. Furthermore, this “borrowing hydrogen” methodology is potentially attractive to pharmaceuticals and industry. This methodology has been applied to the synthesis of some simply pharmaceutical drugs by Williams group[41] and can be further developed in the future.

2.2 Background

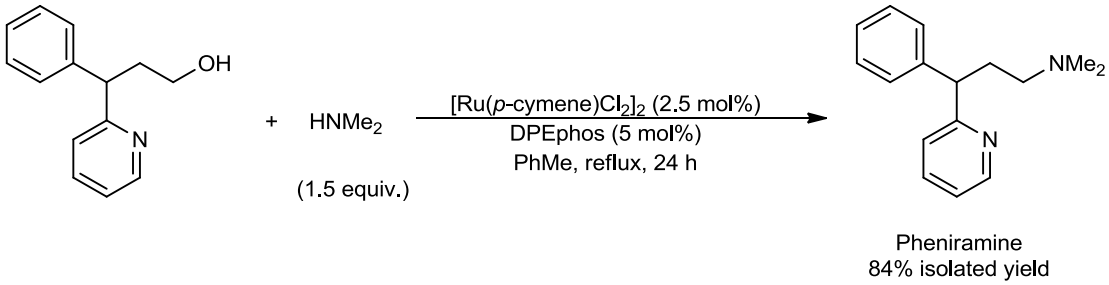
The idea of "catalytic electronic activation" has evolved from previous research by the Williams group which "temporarily enhances the electronic nature of a functional group to a given reaction".[38] They reasoned that if an unreactive substrate **A** could be temporarily activated into electronically activated **A*** towards reaction then the desired bond formation could form the activated intermediate **A***-**B**. By return of **A***-**B** to the initial oxidation level can be yield the desired product **A**-**B**. They termed this concept Catalytic Electronic Activation (Scheme 2.1).[39]



Scheme 2.1. *Catalytic Electronic Activation.*

In 2004, Williams group reported that they used the "borrowing hydrogen" for the formation of C-N bonds *via* aza-Wittig and imine chemistry.[42] Although this method was successful in the synthesis of new C-N bond, it was very difficult to remove all the triphenylphosphine when the reaction was finished. During the reaction imines are formed between an aldehyde or ketone with an amine with the azeotropic removal of water. Afterwards the Williams group proposed to use free amines instead of iminophosphorane and the use of molecular sieves enabled these reactions to achieve high yield.[43] After this method was developed, in 2007 the Williams group reported that they used alcohols as alkylating agents to react with

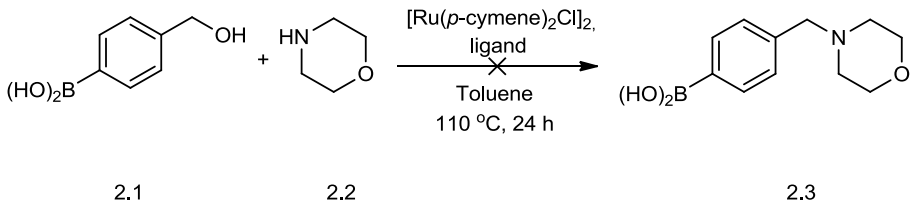
primary amines which were converted into secondary amines by using [Ru(*p*-cymene)Cl_2]$_2$ as catalysts and a bidentate phosphine ligand.[44] They also found that [Ru(*p*-cymene)Cl_2]$_2$/dppf or DPEphos combination is highly efficient for the N-alkylation of secondary amines with primary alcohols by "borrowing hydrogen".[46] They have demonstrated that the use of [Ru(*p*-cymene)Cl_2]$_2$ with either DPEphos or dppf provides a catalyst capable of alkylating amines with alcohols. This chemistry has been applied to the synthesis of some simple pharmaceutical drugs by the Williams group in 2009 (Scheme 2.2).[41]



Scheme 2.2 *N-Alkylation of amines by alcohol in the preparation of Pheniramine.*

2.3 Initial work

In the initial studies, the reaction of boronic acid alcohol **2.1** with morpholine **2.2** was chosen as the first example for the alkylation of an amine with a boronic acid alcohol. Through previous work, [Ru(*p*-cymene)Cl_2]$_2$ was selected as the catalyst, however even additional ligands afforded minimal consumption of starting material after 24 hours at reflux in toluene. None of target amine product **2.3** was observed (Scheme 2.1).

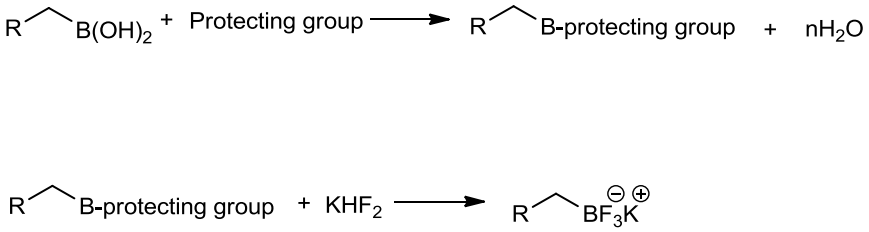


Scheme 2.1. *Reaction of boronic acid alcohol and morpholine in toluene*.

After searching the literature for examples of boronic acid reactions, it was found that boronic acids are often best handled as ester derivatives or organotrifluoroborate salts. Boronic esters are less polar and easier to handle. The hydroxyl group can be exchanged for other substituents which may also provide increased reactivity for several synthetic applications. Boronic esters can also perform as protecting groups to reduce the particular reactivity of boron-carbon bonds to avoid cross-coupling reactions involving the boronic acid. Organotrifluoroborate salts are air-stable boronic acid derivatives that are easy to handle.

The reaction of boronic acid (R = methyl, phenyl) and different kinds of protecting groups were used to form boronic esters. Boronic esters also can be reacted to give

organotrifluoroborate salts (Scheme 2.2). Moreover, all boronic esters and organotrifluoroborate salts are intended for use in further reactions.



Scheme 2.2. *Synthesis of boronic esters and organotrifluoroborate salts*.

Entry	Protecting group	Conversion[a]
1	Pinacol	95%
2	1,8-Diaminonaphthalenene	85%
3	N-Methyldiethanolamine	72%
4	N-Methyliminodiacetic acid	79%
5	1,1,1-tris(Hydroxymethyl) ethane	88%
6	Potassium trifluoride	68%

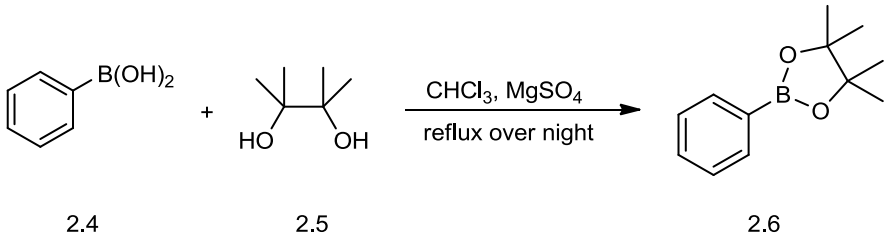
[a] Conversions are based on boronic acid and are determined by ^{1}H NMR analysis.

Table 2.1. *Variation of protecting groups*.

Because most free boronic acid compounds are very difficult to purify and they are often best handled as ester derivatives or organotrifluoroborate salts. Therefore, six protecting groups have been chosen in the reactions to protect the free boronic acid before starting the main reaction.

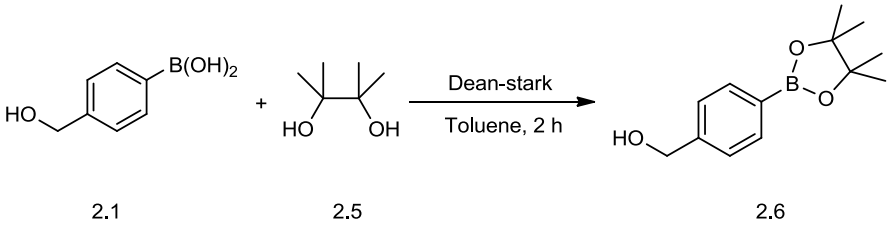
2.4 Borrowing Hydrogen

To continue our optimisation of these reactions we chose to compare the performance of boronic acids and their esters. Most boronic acids exist as colourless crystalline solids that can be handled in air without special precautions. However, the polar nature and some characteristics of boronic acids tend to make their isolation and purification difficult. To lessen these problems, boronic acids are usually purified and characterized as esters. In 1953, Kuicila and co-workers published the first report on the formation of ester **2.4** from phenylboronic acid **2.5** and pinacol **2.6** (Scheme 2.3).



Scheme 2.3. *Synthesis of ester 2.6*.

The synthesis of boronic esters from boronic acids and pinacol is straightforward. However, the overall process is an equilibrium and the forward reaction is favoured when the water produced in the reaction is removed as soon as possible. Ester formation can be aided using a dehydrating agent or Dean-Stark apparatus. In order to reduce the experiment time, a Dean-Stark apparatus was used to form boronic ester **2.6** from boronic acid alcohol **2.1** and pinacol **2.5** (Scheme 2.4).

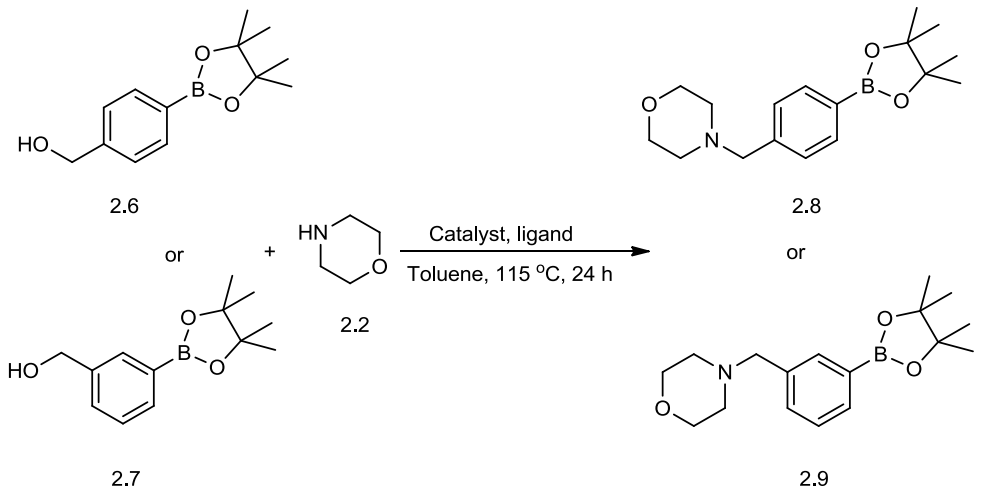


Scheme 2.4. *Synthesis of boronic ester 2.6 by using Dean-stark apparatus*.

A ruthenium-based homogeneous catalytic system was chosen for three reasons: (1)

ruthenium catalysts are relatively cheaper than other transition metal catalysts such as iridium and rhodium, (2) high oxidation state ruthenium catalysts are good mild oxidants for the oxidation of alcohols, with little or no over-oxidation products being obtained, (3) ruthenium catalysts are compatible with many ligands. Additionally, the Williams group has also reported that ruthenium complexes in the presence of dppf or DPEphos are particularly effective for the formation of C-N bonds from alcohols and amines. Complexation of a diphosphine with the ruthenium would lead to the formation of the cationic 18 electron complex [Ru(P-P)(*p*-cymene)Cl]Cl[93] which needs to create a free co-ordination site to become catalytically active. The Williams group[94] has previously shown that the reaction of $[Ru(p\text{-cymene})Cl_2]_2$ with BINAP and the diamine DPEN leads to the formation of the Noyori complex $[Ru(BINAP)(DPEN)Cl_2]$[95] and it is believed that the *p*-cymene is dissociated in the active complex.

Boronic ester alcohols **2.6** or **2.7** were reacted with morpholine **2.2** as a model reaction with various catalysts and ligands to give amine **2.8** or **2.9** in toluene after 24 hours at reflux at 115 ^{O}C (Scheme 2.5).



Scheme 2.5. *Reaction of alcohol and morpholine*.

The results of this reaction with different catalysts and ligands are summarized in

Table 2.2 and 2.3. The % conversions were determined by NMR analysis. In the absence of the catalyst there was 0% conversion into amine **2.8** and **2.9**.

Entry	Catalyst	Mol%	Ligand	Mol% ligand	Conversion Into 2.8 (%)[a]
1	None	-	None	-	0
2	$[Ru(p\text{-cymene})Cl_2]_2$	1	None	-	0
3	$[Ru(p\text{-cymene})Cl_2]_2$	1	DPEphos	2	40
4	$[Ru(p\text{-cymene})Cl_2]_2$	2.5	DPEphos	5	77
5	$[Ru(p\text{-cymene})Cl_2]_2$	1	Dppf	2	16
6	$[Ru(p\text{-cymene})Cl_2]_2$	2.5	Dppf	5	62
7	$[RuCl_2(PPh_3)_3]$	1	None	-	0
8	$[RuCl_2(PPh_3)_3]$	1	DPEphos	1	11
9	$[RuCl_2(PPh_3)_3]$	2.5	DPEphos	2.5	30
10	$[RuCl_2(PPh_3)_3]$	1	Dppf	1	0
11	$[RuCl_2(PPh_3)_3]$	2.5	Dppf	2.5	0

[a] Conversions are based on boronic acid and are determined by ^{1}H NMR analysis.

Table 2.2. *Effect of different catalysts and ligands*.

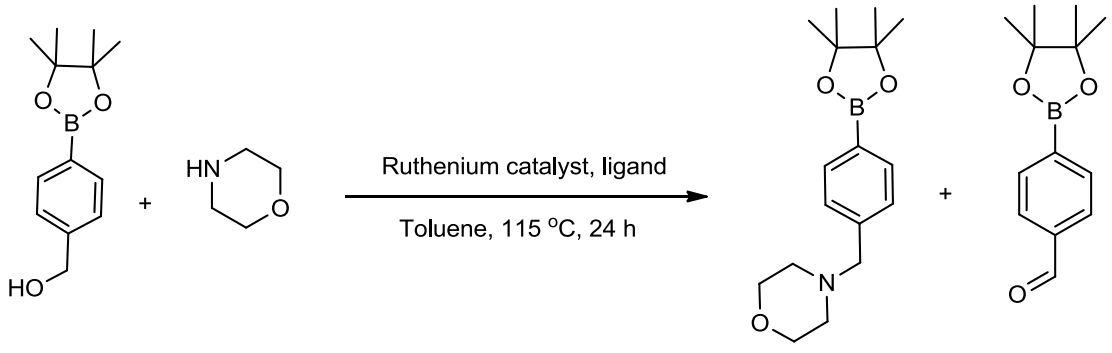
Entry	Catalyst	Mol%	Ligand	Mol% ligand	Conversion Into 2.9 (%)[a]
1	None	-	None	-	0
2	$[Ru(p\text{-cymene})Cl_2]_2$	1	None	-	0
3	$[Ru(p\text{-cymene})Cl_2]_2$	1	DPEphos	2	11
4	$[Ru(p\text{-cymene})Cl_2]_2$	2.5	DPEphos	5	70
5	$[Ru(p\text{-cymene})Cl_2]_2$	1	Dppf	2	0
6	$[Ru(p\text{-cymene})Cl_2]_2$	2.5	Dppf	5	52

7	$[RuCl_2(PPh_3)_3]$	1	None	-	0
8	$[RuCl_2(PPh_3)_3]$	1	DPEphos	1	0
9	$[RuCl_2(PPh_3)_3]$	2.5	DPEphos	2.5	34
10	$[RuCl_2(PPh_3)_3]$	1	Dppf	1	0
11	$[RuCl_2(PPh_3)_3]$	2.5	Dppf	2.5	0

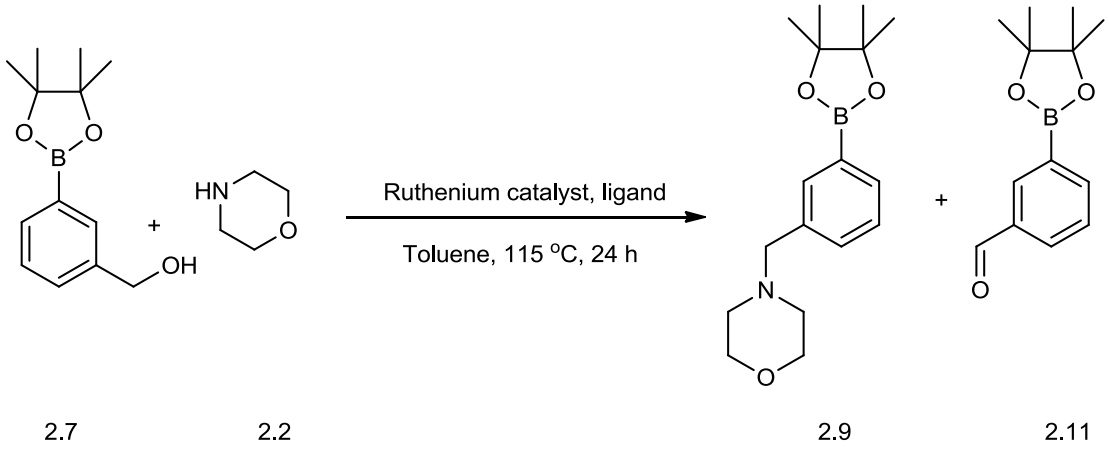
[a] Conversions are based on boronic acid and are determined by ^{1}H NMR analysis.

Table 2.3. *Effect of different catalysts and ligands*.

From table 2.2 and 2.3, target compounds amine **2.8** and **2.9** were formed in 77% and 70% conversion with 2.5 mol% [Ru(*p*-cymene)Cl_2]$_2$ as catalyst and 5 mol% DPEphos as ligand. [Ru(*p*-cymene)Cl_2]$_2$/dppf gave some products as well as the [Ru(*p*-cymene)Cl_2]$_2$/DPEphos catalysts, but the combination of [Ru(*p*-cymene)Cl_2]$_2$ and DPEphos appeared to be the most effective in these reactions and the price of DPEphos is cheaper than Dppf. Herein, it is important to note that 1 mole of [Ru(*p*-cymene)Cl_2]$_2$ provides two moles of ruthenium atoms. Fortunately, only a small amount of aldehyde side product was observed when using ruthenium complex as catalyst in the presence of ligand (Scheme 2.6).



2.6 2.2 2.8 2.10



2.7 2.2 2.9 2.11

Scheme 2.6. *Reaction of alcohol and morpholine*.

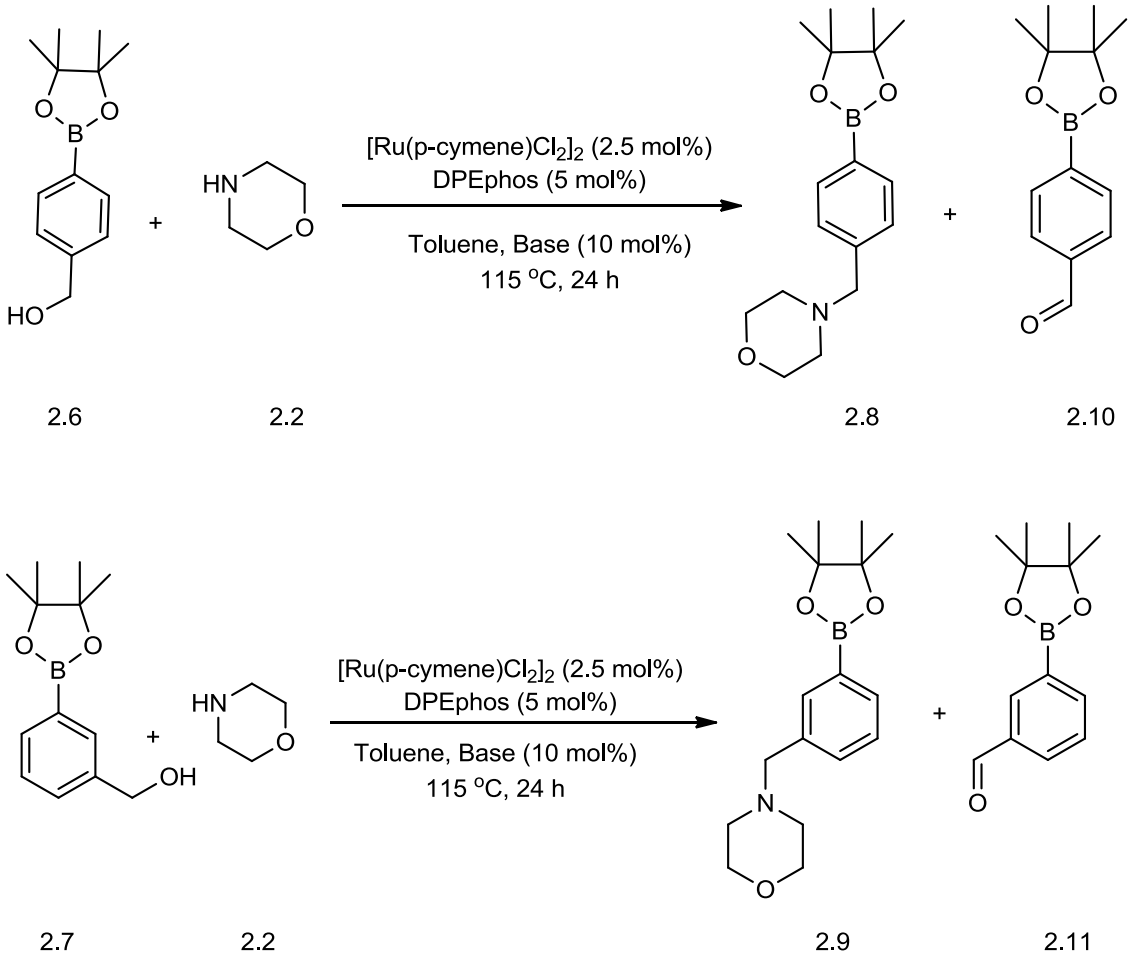
Entry	Catalyst	Mol%	Ligand	Mol% ligand	Amine 2.8 (%)	Aldehyde 2.10 (%)
1	[Ru(*p*-cymene)Cl_2]$_2$	2.5	DPEphos	5	77	4
2	[Ru(*p*-cymene)Cl_2]$_2$	2.5	Dppf	5	62	11
3	[$RuCl_2(PPh_3)_3$]	2.5	DPEphos	2.5	30	15

Table 2.4. Results for the reaction of alcohol **9** and morpholine **2**

Entry	Catalyst	Mol%	Ligand	Mol% ligand	Amine 2.9 (%)	Aldehyde 2.11 (%)
1	[Ru(*p*-cymene)Cl_2]$_2$	2.5	DPEphos	5	70	6
2	[Ru(*p*-cymene)Cl_2]$_2$	2.5	Dppf	5	52	20
3	[$RuCl_2(PPh_3)_3$]	2.5	DPEphos	2.5	34	26

Table 2.5. *Results for the reaction of alcohol and morpholine*.

It is interesting to discover that without base, the reaction also went almost to completion (Table 2.4, entry 1 and Table 5 entry 1). Subsequently, the effect of different bases was then carried out using the [Ru(*p*-cymene)Cl_2]$_2$/DPEphos combination (Scheme 2.7).



Scheme 2.7. *Results for base screening for the reaction of alcohol 2.7 and morpholine*.

Entry	Base	Amine 2.8 (%)	Aldehyde 2.10 (%)
1	$NaHCO_3$	80	2
2	Na_2CO_3	89	0
3	K_2CO_3	74	8
4	NaO_2CCH_3	34	11
5	Et_3N	0	38

Table 2.6. *Effect of addition of 10mol% base in synthesis of amine 2.8*.

Entry	Base	Amine 2.9 (%)	Aldehyde 2.11 (%)
1	$NaHCO_3$	44	13
2	Na_2CO_3	81	0

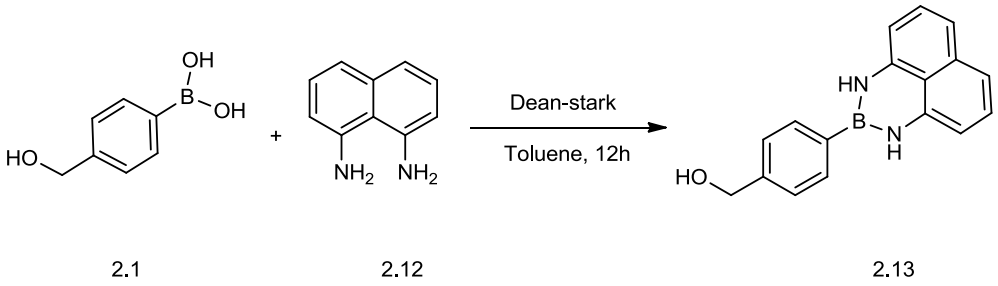
3	K_2CO_3	61	10
4	NaO_2CCH_3	37	8
5	Et_3N	0	21

Table 2.7. *Effect of addition of 10mol% base in synthesis of amine*.

The results of these reactions show NaO_2CCH_3 and Et_3N give poor yields, but Et_3N favours the formation of the aldehyde (Table 2.6, entry 5 and Table 2.7, entry 5) whilst Na_2CO_3 is suitable as a base for both reactions. $NaHCO_3$ and K_2CO_3 are suitable for forming amine **2.8** as well, but the reaction did not go to completion (Table 2.6, entry 1 and 3).

DPEphos as ligand and Na_2CO_3 as base with $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst appear to favour the formation of the boronic ester amine. We then decided to examine different protecting groups, in order to determine whether any increase in yield of the boronic ester amine could be achieved.

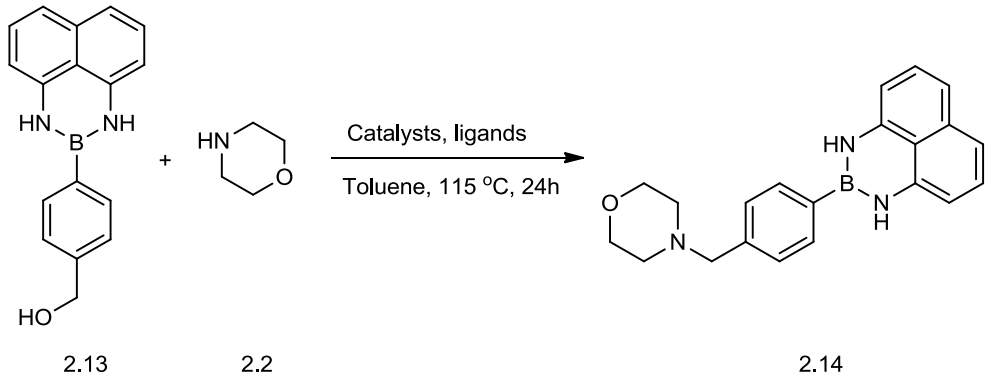
1,8-Diaminonaphthalene seemed to be a good candidate for the protecting group since the nitrogen atoms donate their lone pair electrons to the vacant p-orbital of the boron atom and potentially increase overall stability. There are three advantages to the use of 1,8-diaminonaphthalene as protecting group: (1) ease of introduction, (2) high stability during coupling and isolation processes, (3) simple deprotection. Boronic ester alcohol **2.1** was treated with 1,8-diaminonaphthalene **2.12** in toluene at reflux, with Dean-Stark apparatus to remove water, affording the corresponding diazaborinine **2.13** in high yield (Scheme 2.8).



2.1 2.12 2.13

Scheme 2.8. *Synthesis of diazaborinine 2.13*.

Diazaborinine alcohol **2.13** was treated with morpholine **2.2** in the presence of catalyst and ligands to give amine **2.14** in toluene after 24 hours at reflux at 115 ^{o}C (Scheme 2.9).



2.13 2.2 2.14

Scheme 2.9. *Reaction of alcohol 2.13 and morpholine*.

The results of this reaction with different catalysts and ligands are summarized in Table 2.8. Conversions were determined by NMR analysis. In the absence of the catalyst there was 0% conversion into amine **2.14**.

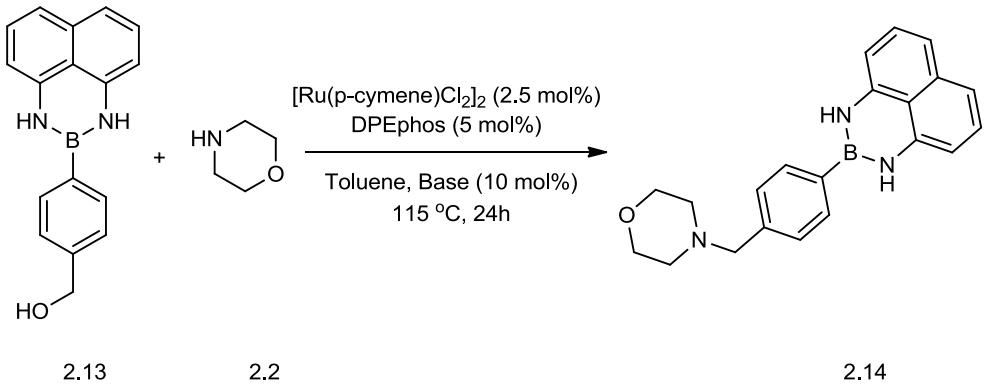
Entry	**Catalyst**	**Mol%**	**Ligand**	**Mol% ligand**	**Conversion Into 2.14 (%)[a]**
1	None	-	None	-	0
2	$[Ru(p\text{-cymene})Cl_2]_2$	1	None	-	0
3	$[Ru(p\text{-cymene})Cl_2]_2$	1	DPEphos	2	0
4	$[Ru(p\text{-cymene})Cl_2]_2$	2.5	DPEphos	5	33
5	$[Ru(p\text{-cymene})Cl_2]_2$	1	Dppf	2	0
6	$[Ru(p\text{-cymene})Cl_2]_2$	2.5	Dppf	5	19
7	$[RuCl_2(PPh_3)_3]$	1	None	-	0
8	$[RuCl_2(PPh_3)_3]$	1	DPEphos	1	0
9	$[RuCl_2(PPh_3)_3]$	2.5	DPEphos	2.5	0
10	$[RuCl_2(PPh_3)_3]$	1	Dppf	1	0

11	$[RuCl_2(PPh_3)_3]$	2.5	Dppf	2.5	0

[a] Conversions are based on diazaborinine and are determined by ^{1}H NMR analysis.

Table 2.8. *Effect of different catalysts and ligands*.

The results of these reactions show that this protecting group is not as good as pinacol, but the conversion of amine **2.14** was still obtained using DPEphos as ligand with $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst. The experiments were repeated using $[Ru(p\text{-cymene})Cl_2]_2$ and DPEphos and a variety of bases, to examine the effect upon the reaction (Scheme 2.10, Table 2.9).



2.13 2.2 2.14

Scheme 2.10. *Results for screening for the reaction of alcohol 2.13 and morpholine*.

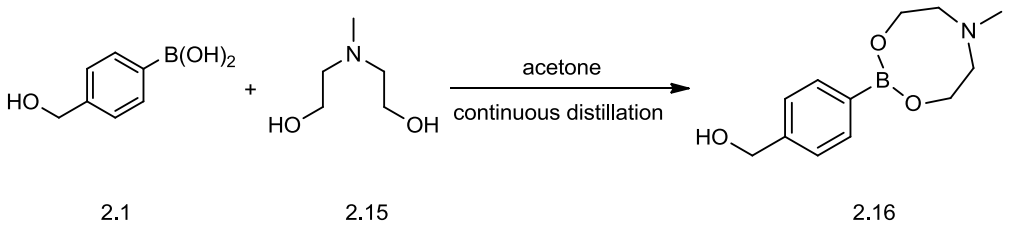
Entry	Base	Amine 2.14 (%)
1	$NaHCO_3$	14
2	Na_2CO_3	40
3	K_2CO_3	9
4	NaO_2CCH_3	0
5	Et_3N	0

Table 2.9. *Effect of addition of 10mol% base in synthesis of amine 2.14*.

The results of these reactions show almost all bases perform poorly in the reaction, with Na_2CO_3 giving only slightly increased conversion of amine **2.14**. Under same reaction conditions, but with increased reaction time to 48 hours, the conversion was

also not changed; 1,8-diaminonaphthalene was not taken any further as a protecting group in this reaction.

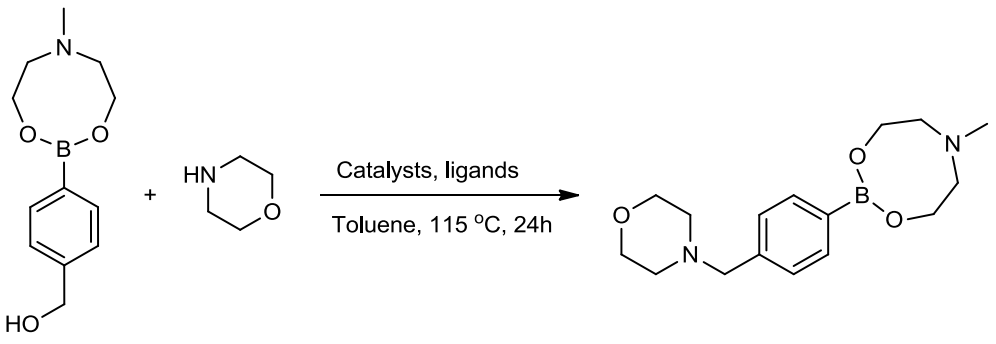
N-Methyldiethanolamine, the third protecting group, was then considered. The nitrogen atoms on N-methyldiethanolamine can donate their lone pair electrons to the vacant p-orbital of the boron atom, and formation of boronic ester alcohol **2.16** was more soluble in hot toluene (Scheme 2.11).



2.1 2.15 2.16

Scheme 2.11. *Synthesis of boronate 2.16*.

Boronic ester alcohol **2.16** was treated with morpholine **2.2** in the presence of catalyst and ligands to give amine **2.17** in toluene after 24 hours at reflux at 115 ^{O}C (Scheme 2.12).



2.16 2.2 2.17

Scheme 2.12. *Reaction of boronate 2.16 and morpholine*.

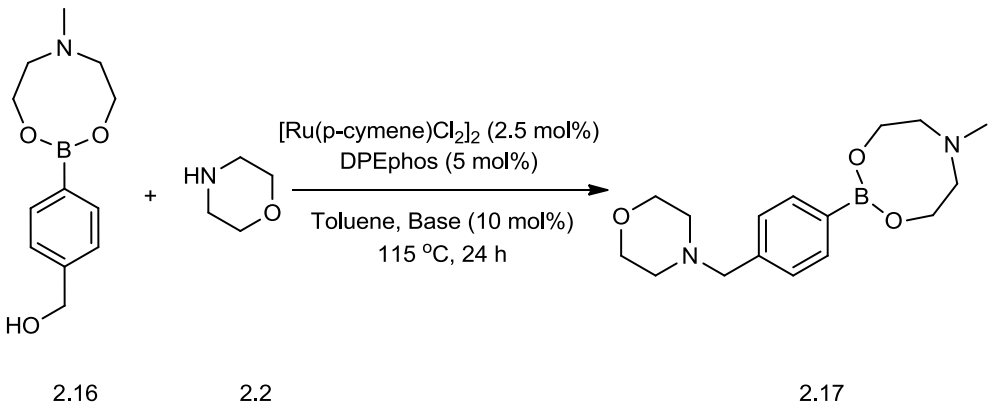
The results of this reaction with different catalysts and ligands are summarized in Table 2.10. Conversions were determined by NMR analysis. In the absence of the

catalyst there was 0% conversion into amine **2.17**.

Entry	Catalyst	Mol%	Ligand	Mol% ligand	Conversion Into 2.17 (%)[a]
1	None	-	None	-	0
2	$[Ru(p\text{-cymene})Cl_2]_2$	1	None	-	0
3	$[Ru(p\text{-cymene})Cl_2]_2$	1	DPEphos	2	10
4	$[Ru(p\text{-cymene})Cl_2]_2$	2.5	DPEphos	5	41
5	$[Ru(p\text{-cymene})Cl_2]_2$	1	Dppf	2	0
6	$[Ru(p\text{-cymene})Cl_2]_2$	2.5	Dppf	5	27
7	$[RuCl_2(PPh_3)_3]$	1	None	-	0
8	$[RuCl_2(PPh_3)_3]$	1	DPEphos	1	0
9	$[RuCl_2(PPh_3)_3]$	2.5	DPEphos	2.5	12
10	$[RuCl_2(PPh_3)_3]$	1	Dppf	1	0
11	$[RuCl_2(PPh_3)_3]$	2.5	Dppf	2.5	0

[a] Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

Table 2.10. *Effect of different catalysts and ligands*.



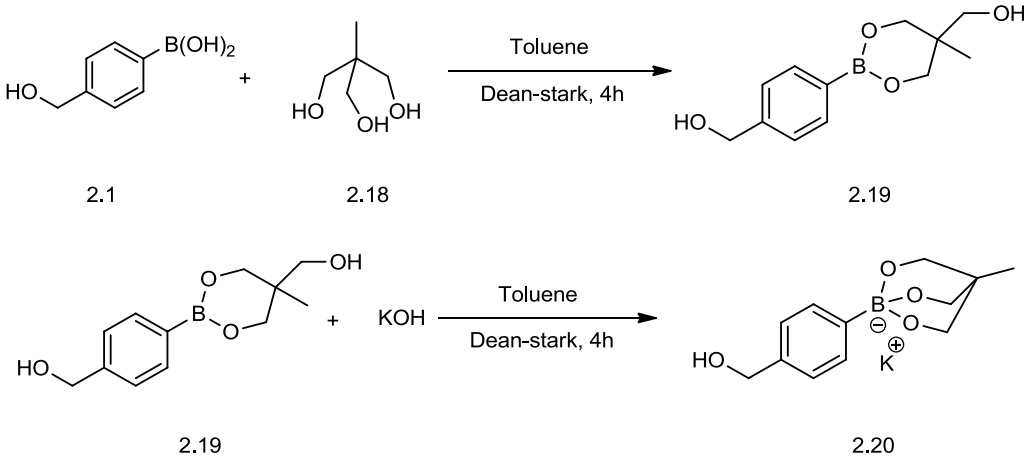
Scheme 2.13. *Results for screening for the reaction of alcohol 2.16 and morpholine*.

Entry	Base	Amine 2.17 (%)
1	$NaHCO_3$	28
2	Na_2CO_3	58
3	K_2CO_3	17
4	NaO_2CCH_3	0
5	Et_3N	0

Table 2.11. *Effect of addition of 10mol% base in synthesis of amine 2.17*.

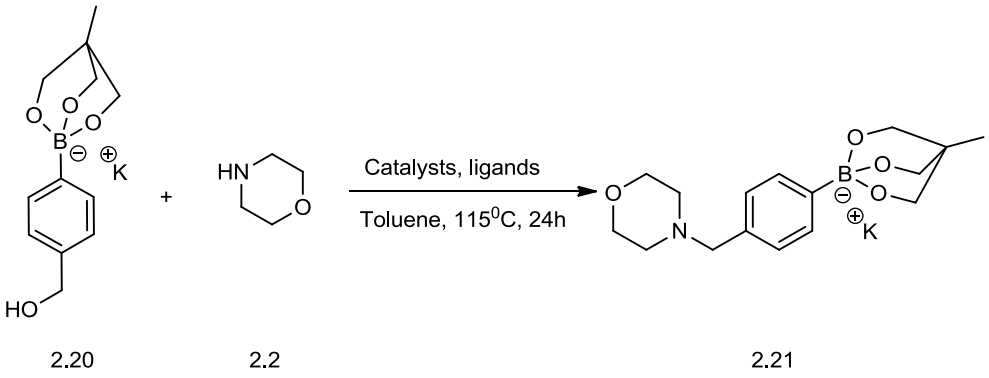
From the results in Table 2.10 and 2.11, $[Ru(p\text{-cymene})Cl_2]_2$/DPEphos/$Na_2CO_3$ system gave 58% conversion into the amine **2.17**. Relative to the use of 1,8-diaminonaphthalene as a protecting group, using N-methyldiethanolamine, the conversion into amine **2.17** was increased, but showed no improvement over pinacol as a protecting group.

1,1,1-tris(Hydroxymethyl) ethane was then chosen as the next protecting group. We heat boronic acids with 1,1,1-tris(hydroxymethyl) ethane for 4 hours under Dean-Stark conditions and then we found it gives the dioxaborinane intermediate **2.19** first. Following heating for another 4 hours with KOH under Dean-Stark conditions gives the compound **2.20**. which were purified by flash column chromatography. This alcohol was stable to benchtop storage and easily hydrolysed using mild conditions to liberate the corresponding boronic acids (Scheme 2.14).



Scheme 2.14. *Synthesis of potassium triolborate 2.20*.

Potassium triolborate **2.20** was treated with morpholine **2.2** in the presence of catalysts and ligands to give amine **2.21** in toluene after 24 hours at reflux at 115 ^{O}C (Scheme 2.15).



2.20 2.2 2.21

Scheme 2.15. *Reaction of potassium triolborate 2.21 and morpholine*.

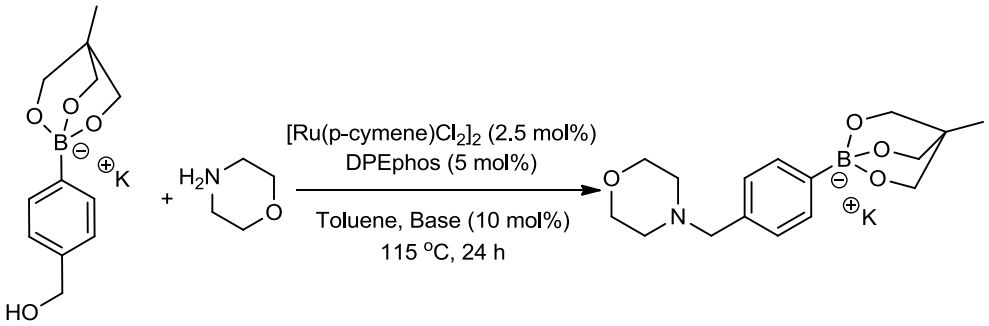
The results of this reaction with different catalysts and ligands are summarized in Table 2.12. Conversions were determined by NMR analysis. In the absence of the catalyst there was 0% conversion into amine **2.21**.

Entry	**Catalyst**	**Mol%**	**Ligand**	**Mol% ligand**	**Conversion Into 2.21 (%)[a]**
1	None	-	None	-	0
2	[Ru(*p*-cymene)Cl_2]$_2$	1	None	-	0
3	[Ru(*p*-cymene)Cl_2]$_2$	1	DPEphos	2	0
4	[Ru(*p*-cymene)Cl_2]$_2$	2.5	DPEphos	5	11
5	[Ru(*p*-cymene)Cl_2]$_2$	1	Dppf	2	0
6	[Ru(*p*-cymene)Cl_2]$_2$	2.5	Dppf	5	0
7	[$RuCl_2(PPh_3)_3$]	1	None	-	0
8	[$RuCl_2(PPh_3)_3$]	1	DPEphos	1	0
9	[$RuCl_2(PPh_3)_3$]	2.5	DPEphos	2.5	0

10	$[RuCl_2(PPh_3)_3]$	1	Dppf	1	0
11	$[RuCl_2(PPh_3)_3]$	2.5	Dppf	2.5	0

[a] Conversions are based on boronic acid and are determined by ^{1}H NMR analysis.

Table 2.12. *Effect of different catalysts and ligands*.



2.20 2.2 2.21

Scheme 2.16. *Results for screening for the reaction of potassium triolborate 2.20 and morpholine*.

Entry	Base	Amine 2.21 (%)
1	$NaHCO_3$	0
2	Na_2CO_3	18
3	K_2CO_3	0
4	NaO_2CCH_3	0
5	Et_3N	0

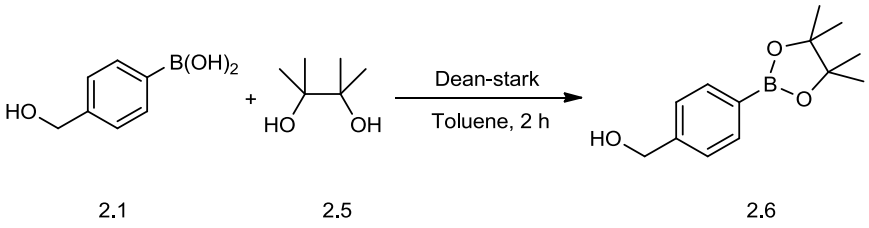
Table 2.13. *Effect of addition of 10mol% base in synthesis of amine 2.21*.

It can be seen that for the reaction of potassium triolborate **2.20** and morpholine **2.2**, conversion of amine **2.21** was almost as same as amine **2.14**. It was shown that this protecting group, 1,1,1-tris(hydroxymethyl) ethane, was inefficient for the "borrowing hydrogen" reaction.

The next strategy was to run the reaction using potassium trifluoroborate as starting material. Generally, boronic acids must be protected during the usual syntheses. Deprotection often results in low purity compounds and is reliant on multiple

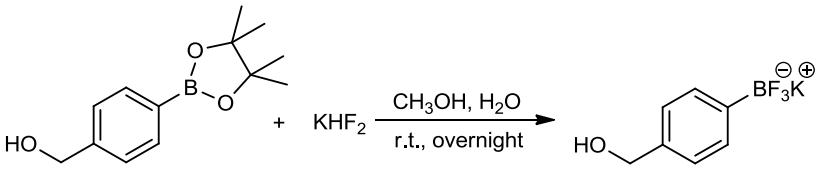
extractions or chromatographic techniques to isolate products. The strategy of deprotecting a pinacol boronic ester to its corresponding potassium trifluoroborate seemed attractive, as potassium trifluoroborates can be suitable to use under high temperatures and catalysts conditions. Moreover, potassium trifluoroborates can be converted into the corresponding boronic acid compounds easily by using lithium hydroxide in acetonitrile and water.

Step 1



2.1 2.5 2.6

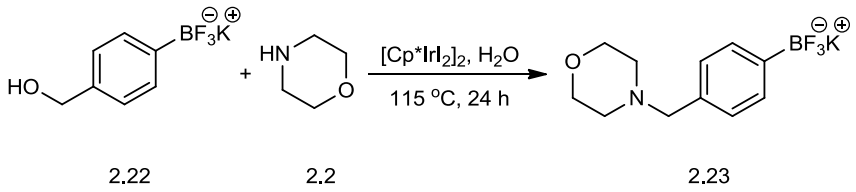
Step 2



2.6 2.22

Scheme 2.17. *Synthesis of potassium trifluoroborate 2.22*.

Potassium trifluoroborate **2.22** does not dissolve in common organic solvents, such as toluene, and requires polar solvents such as water as solvent and therefore a change in the catalyst and ligand system. We were decided to use $[Cp^*IrI_2]_2$ as catalyst, which has been used for "borrowing hydrogen" reaction successfully. $[Cp^*IrI_2]_2$ was an effective catalyst for alkalation of amines with alcohols when water is used as solvent. Importantly the reaction has no requirement for the addition of ligand or any base to activate the catalyst.



2.22 2.2 2.23

Scheme 2.18. *Reaction of Potassium trifluoroborate 2.22 and morpholine*.

The result of this reaction with $[Cp^*IrI_2]_2$ as catalyst is summarized in Table 2.14. Conversions were determined by NMR analysis.

Entry	Catalyst (1 mol%)	Solvent	Conversion into 2.23 (%)[a]
1	$[Cp^*IrI_2]_2$	H_2O	0

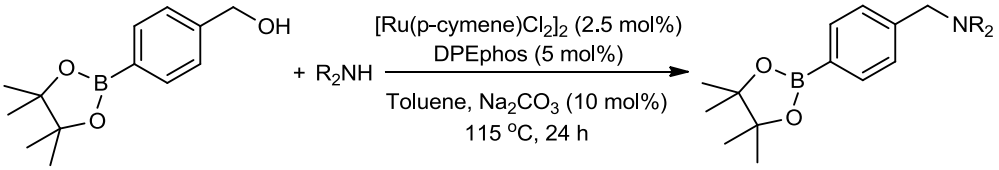
[a] Conversions are based on trifluoroborate and are determined by ^{1}H NMR analysis.

Table 2.14. *Effect of $[Cp^*IrI_2]_2$ catalysts*.

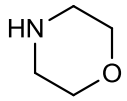
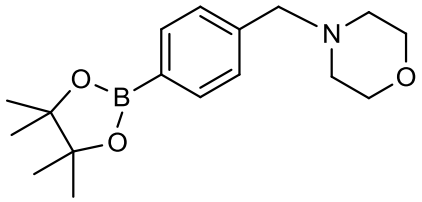
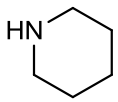
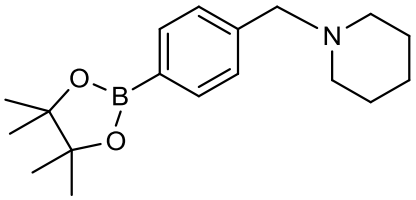
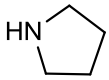
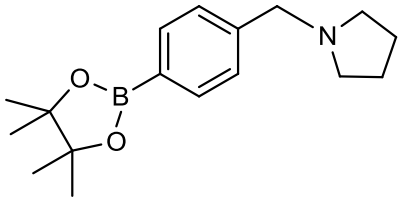
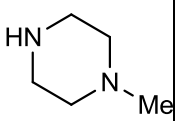
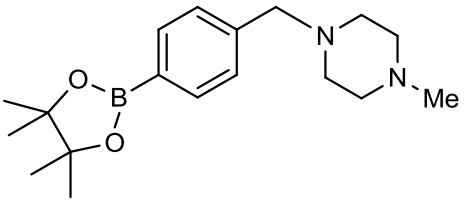
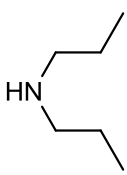
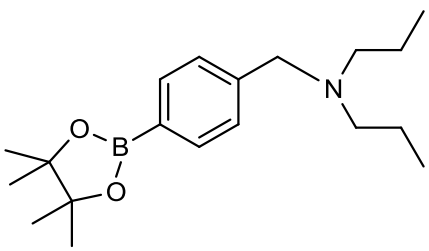
The results of this reaction show potassium trifluoroborate **2.22** was not a suitable compound for the N-alkylation of amines with alcohol under the $[Cp^*IrI_2]_2$ catalysis conditions.

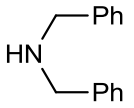
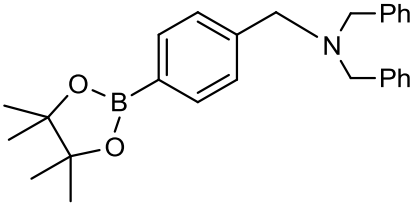
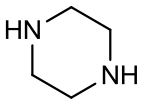
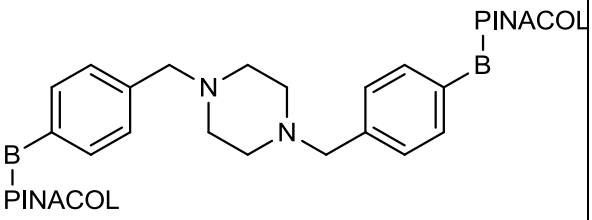
From these results, it was determined that pinacol was the best protecting group, and that a catalyst loading of 5 mol% ruthenium (i.e. 2.5 mol% of $[Ru(p\text{-cymene})Cl_2]_2$), 5 mol% DPEphos and Na_2CO_3 as base was found to be optimal for the N-alkylation of boronic ester alcohol with secondary amine by the borrowing hydrogen method. In order to show the general applicability of this method for the N-alkylation of alcohol with amine, a number of examples of the synthesis of para- and meta- boronic ester alcohol with primary and secondary amine were carried out using the optimised conditions and these findings have been reported recently. The para- and meta- boronic alcohol with morpholine was achieved in good yield (Table 6 and 7). The next step was to employ different secondary amines to react with para-

and meta-boronic alcohol (Scheme 2.19 and 2.20, Table 2.13 and 2.14).



Scheme 2.19. *Para-boronic alcohol reaction with secondary amines*.

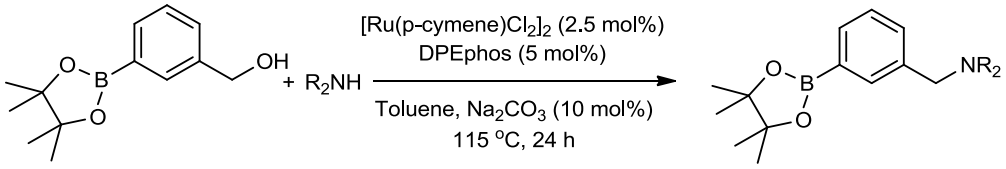
Entry	Starting amine		Product	Conversion (%)[a]
1		**2.8**		89
2		**2.24**		83
3		**2.25**		77
4		**2.26**		84
5		**2.27**		87

6		**2.28**		57
7[b]		**2.29**		61

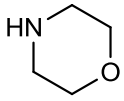
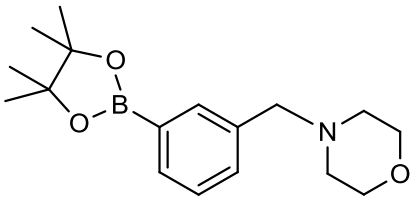
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1); Conversions are based on boronic acid and are determined by ^{1}H NMR analysis.

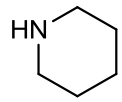
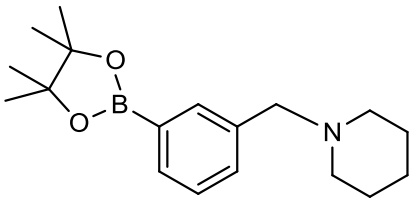
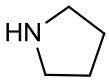
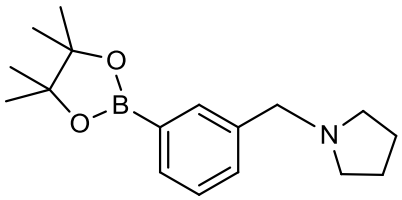
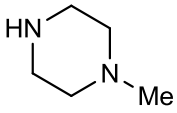
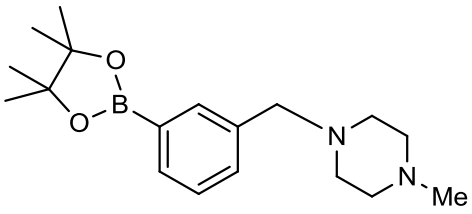
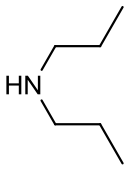
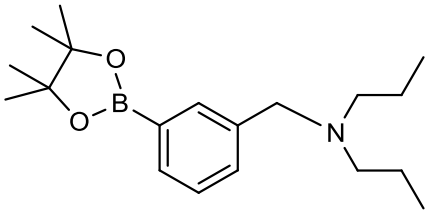
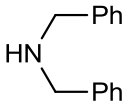
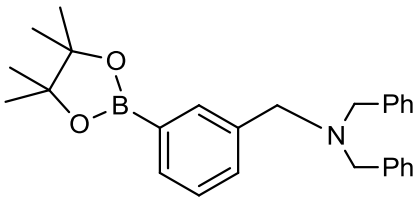
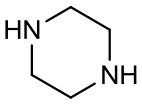
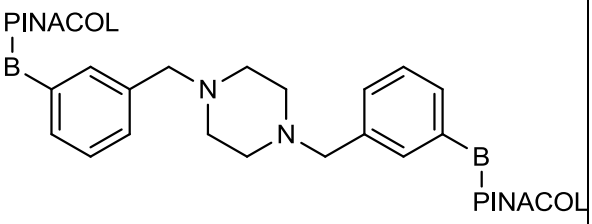
[b] alcohol:amine (2:1), 5 mol% Ru, 10 mol% DPEphos and 20 mol% base

Table 2.13. *Variation of secondary amine with para-boronic alcohols*.



Scheme 2.20. *Meta-boronic alcohol reaction with secondary amines*.

Entry	**Starting amine**		**Product**	**Conver-sion (%)[a]**
1		**2.9**		81

2		**2.30**		79
3		**2.31**		75
4		**2.32**		77
5		**2.33**		71
6		**2.34**		55
7[b]		**2.35**		60

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1); Conversions are based on boronic acid and are determined by ^{1}H NMR analysis.

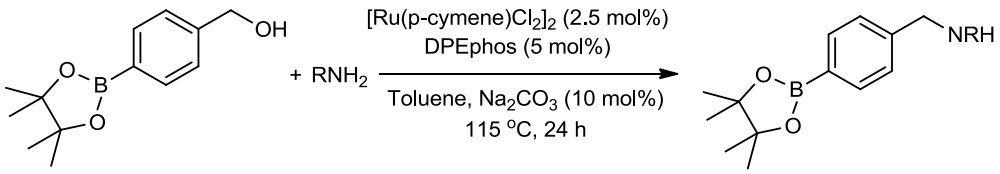
[b] alcohol:amine (2:1), 5 mol% Ru, 10 mol% DPEphos and 20 mol% base

Table 2.14. *Variation of secondary amines with meta-boronic alcohols*.

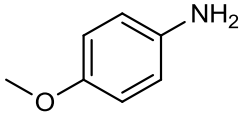
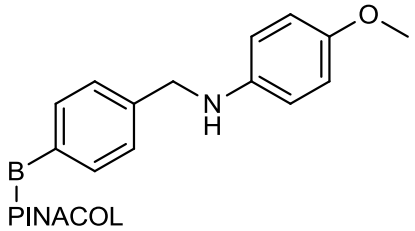
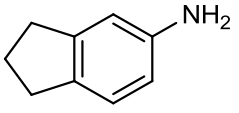
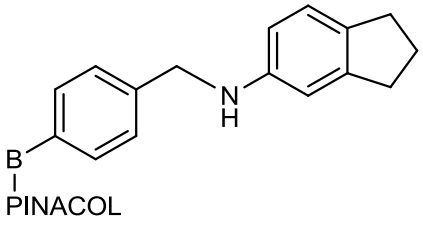
Pleasingly, all reactions were successful under the borrowing hydrogen conditions.

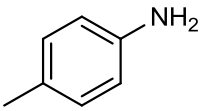
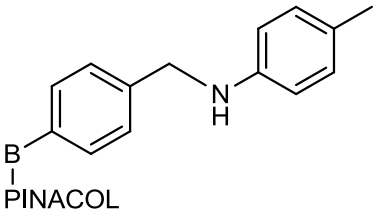
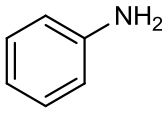
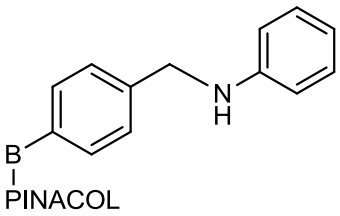
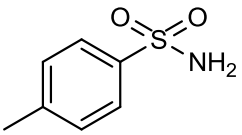
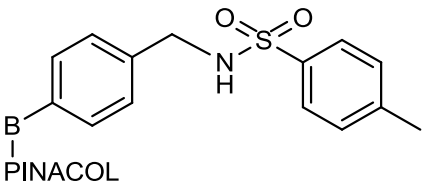
Reactions were successful for the alkylation of both cyclic (Table 2.13, entries 1-4 and Table 2.14, entries 1-4) and acyclic (Table 2.13, entry 5 and Table 2.14 entry 5) amines with the prospective of dibenzylamine (Table 2.13, entry 6 and Table 2.14 entry 6) and piperazine (Table 2.13, entry 7 and Table 2.14, entry 7). Piperazine was an interesting example of the scope of this reaction, requiring two portions of boronic ester alcohol and double amount of catalysts, ligands and bases, forming a symmetrical product (Table 2.13, entry 7 and Table 2.14, entry 7).

The next strategy was to use para- and meta-boronic alcohols react with a range of primary amines (Scheme 2.21 and 2.22, Table 2.15 and 2.16).



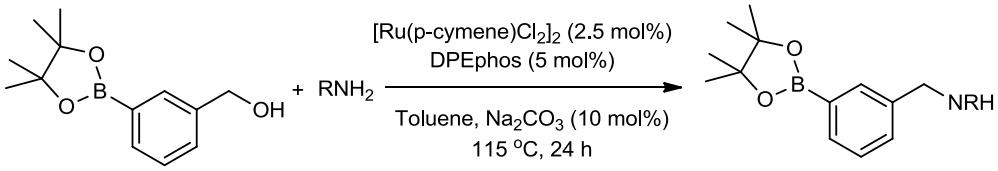
Scheme 2.21. *Para-boronic alcohol reacting with primary amines*.

Entry	Starting amine		Product	Conversion (%)[a]
1		**2.36**		61
2		**2.37**		54

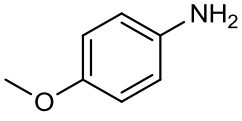
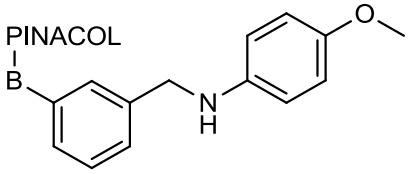
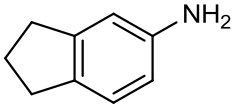
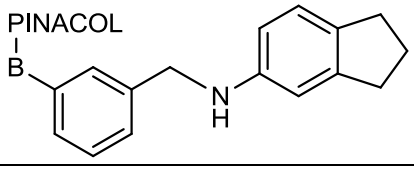
3		**2.38**		53
4		**2.39**		12
5		**2.40**		0

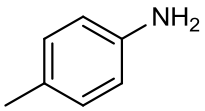
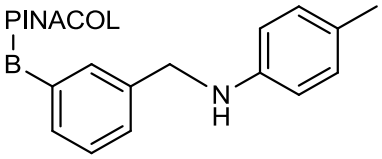
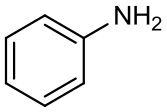
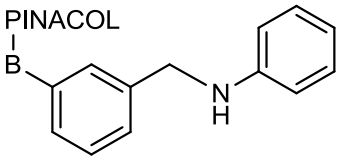
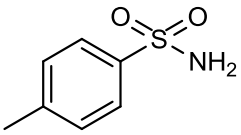
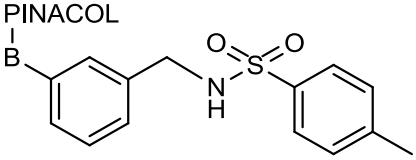
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

Table 2.15. *Variation of primary amines with para-boronic alcohols*.



Scheme 2.22. *Meta-boronic alcohol reaction with primary amines.*

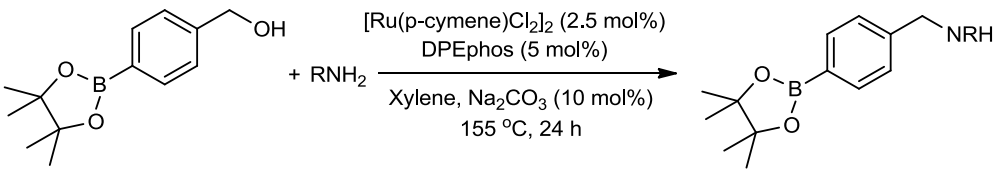
Entry	Starting amine		Product	Conversion (%)[a]
1		**2.41**		59
2		**2.42**		60

3		**2.43**		41
4		**2.44**		0
5		**2.45**		0

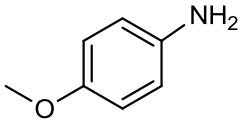
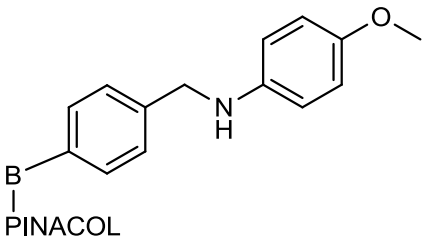
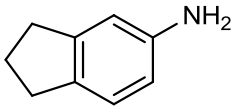
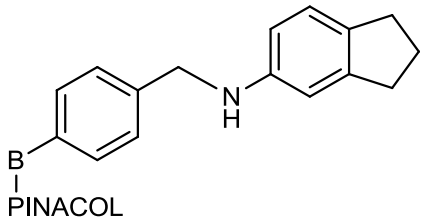
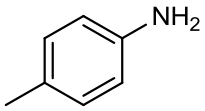
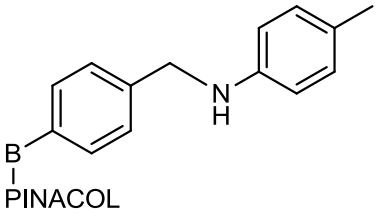
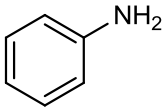
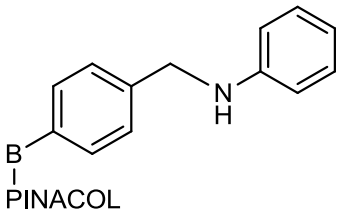
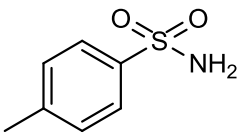
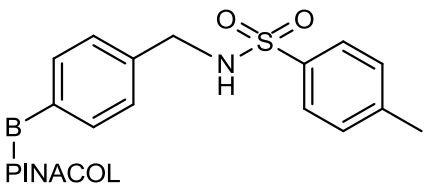
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

Table 2.16. *Variation of primary amines with meta-boronic alcohols*.

It was surprising to find that para- and meta-boronic acid alcohols react with a range of primary amines to only give relatively low conversions under Ru/DPEphos/Na_2CO_3 conditions. Boronic acid alcohol with aniline and 4-methylbenzenesulfonamide gave a low conversion of 12% and even no product was formed (Table 2.15, entries 4-5 and Table 2.16, entries 4-5). Comparing *p*-toluidine wih aniline, there are two possible reasons to cause aniline gave a low conversion and even no product was formed. Firstly, the methyl group on *p*-toluidine was a donating group and it will cause amine on *p*-toluidine ti be more reactive than aniline. Secondly, aniline has the lone pair of electrons on the nitrogen which can be delocalised into the benzene ring and make the para-position more reactive. However, the para-position on *p*-toluidine has been inhibiting by a methyl group. Afterwards, it was decided to double the amount of amine, under the same conditions, but this did not improve the level of conversion. Finally, it was decided to run reactions under the Ru/DPEphos/Na_2CO_3 conditions at a high temperature of 155 ^{o}C using xylene as the solvent. All results are shown below (Scheme 2.23 and 2.24, Table 2.17 and 2.18).

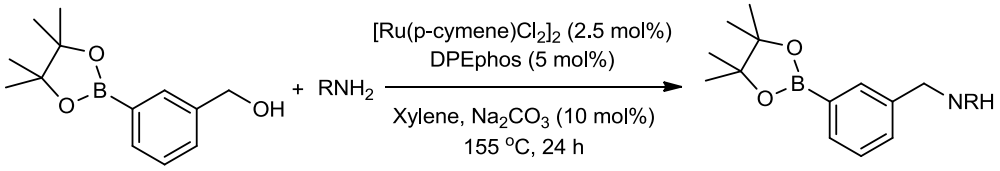


Scheme 2.23. *Para-boronic alcohol reaction with primary amines*.

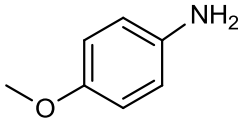
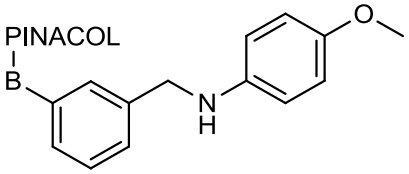
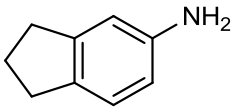
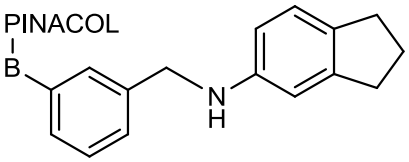
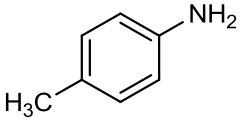
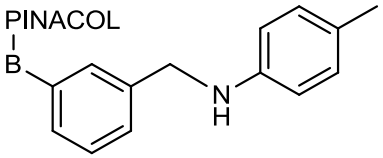
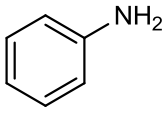
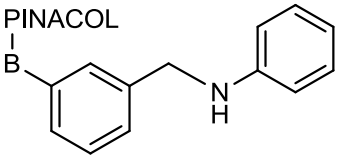
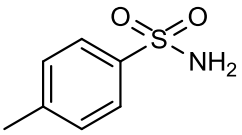
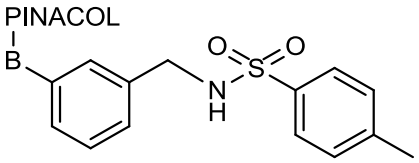
Entry	Starting amine		Product	Isolated yield (%)[a]
1		**2.36**		72
2		**2.37**		72
3		**2.38**		70
4		**2.39**		52
5		**2.40**		0

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

Table 2.17. *Variation of* primary amines with meta-boronic alcohols



Scheme 2.24. *Meta-boronic alcohol reaction with primary amines.*

Entry	Starting amine		Product	Isolated yield (%)[a]
1		**2.41**		66
2		**2.42**		71
3		**2.43**		62
4		**2.44**		43
5		**2.45**		0

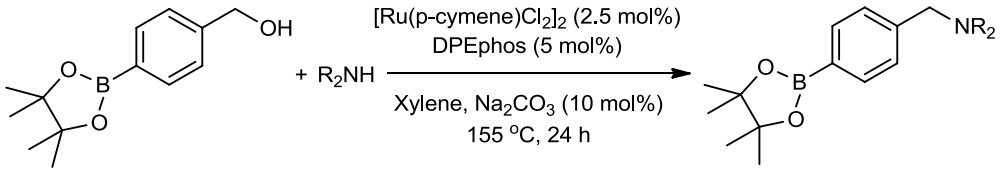
[a] Reactions carried out on 1 mmol in xylene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

Table 2.18. *Variation of primary amines with meta-boronic alcohols*.

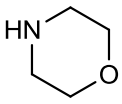
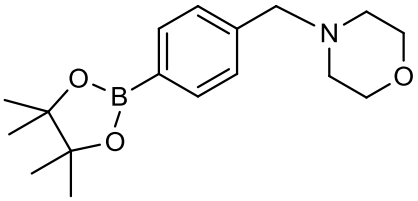
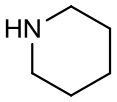
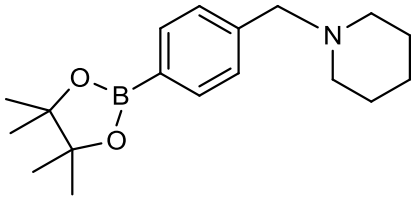
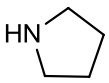
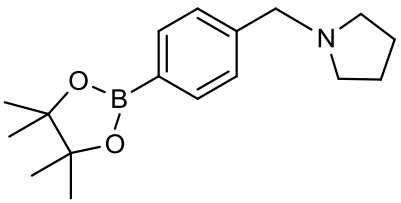
From these results, we found that these N-alkylation reactions were more suitable to reaction under high temperatures and this was presumably due to an increase in the catalysts' activity and the basicity of amines which made amines able to act as a

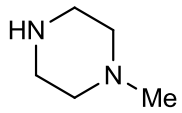
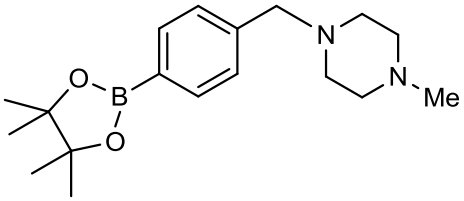
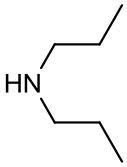
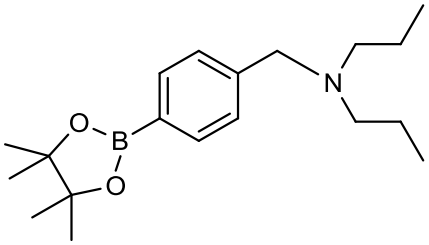
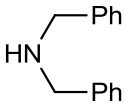
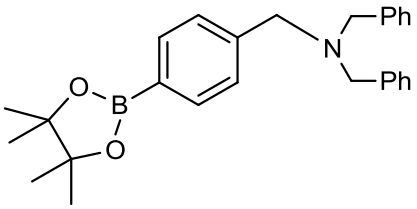
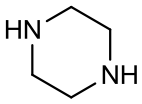
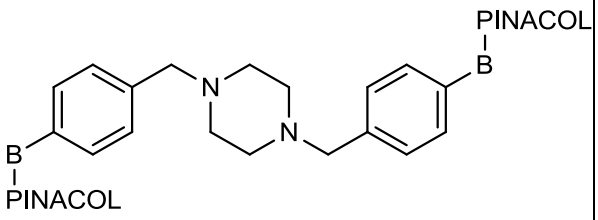
nucleophile in the reaction. All products were isolated and purified by recrystallisation in good yields. Some low conversions were obtained, leading to a lower isolated yield and this is possibly due to the amine coordination to the catalyst as a ligand in the reaction.

The alkylation of different secondary amines with para- and meta-boronic acid alcohols under Ru/DPEphos/Na_2CO_3 conditions at a high temperature of 155 ^{o}C using xylene as the solvent was examined. All results are shown below (Scheme 2.25 and 2.26, Table 2.19 and 2.20).



Scheme 2.25. *Para-boronic alcohol reaction with secondary amines*.

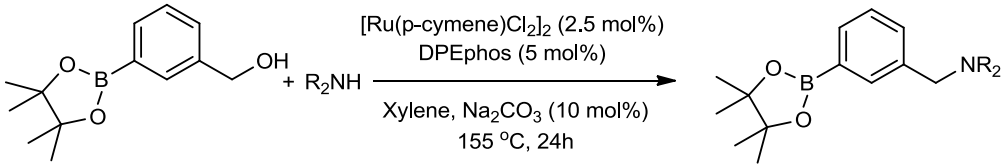
Entry	Starting amine		Product	Isolated yield (%)[a]
1		**2.8**		84
2		**2.24**		80
3		**2.25**		75

4		**2.26**		83
5		**2.27**		87
6		**2.28**		59
7[b]		**2.29**		65

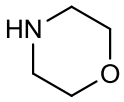
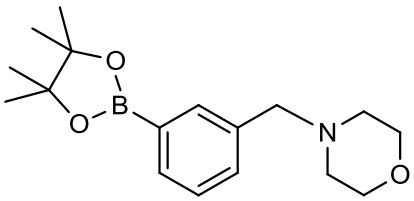
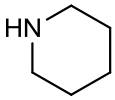
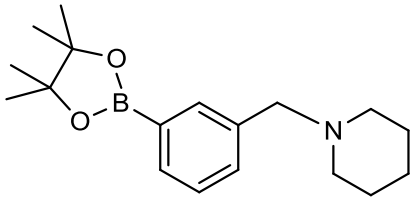
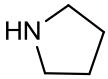
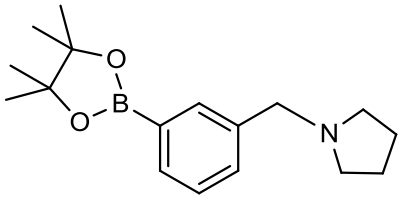
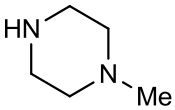
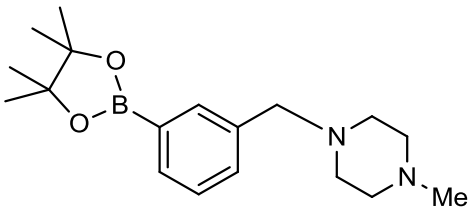
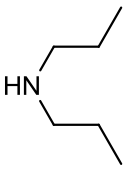
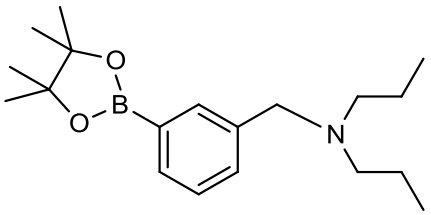
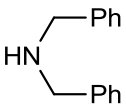
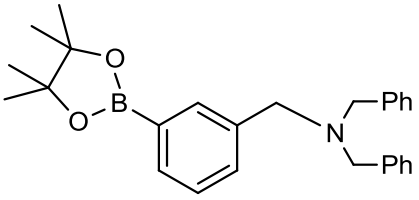
[a] Reactions carried out on 1 mmol in xylene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

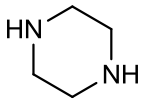
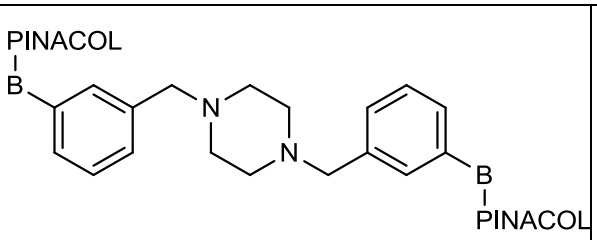
[b] alcohol:amine (2:1), 5 mol% Ru, 10 mol% DPEphos and 20 mol% base

Table 2.19. *Variation of secondary amines with para-boronic alcohols*.



Scheme 2.26. *Meta-boronic alcohol reaction with secondary amines*.

Entry	Starting amine		Product	Isolated yield (%)[a]
1		**2.9**		80
2		**2.30**		79
3		**2.31**		78
4		**2.32**		80
5		**2.33**		69
6		**2.34**		65

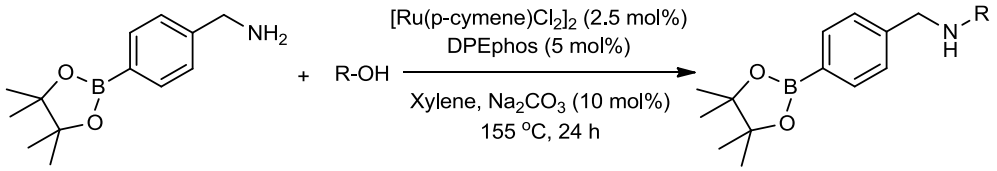
7[b]		**2.35**		60

[a] Reactions carried out on 1 mmol in xylene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

[b] alcohol:amine (2:1), 5 mol% Ru, 10 mol% DPEphos and 20 mol% base

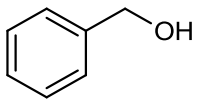
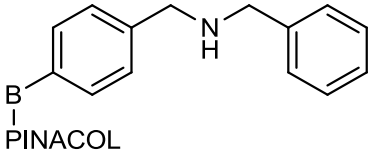
Table 2.20. *Variation of secondary amines with meta-boronic alcohols*.

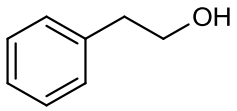
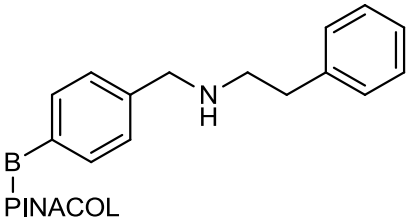
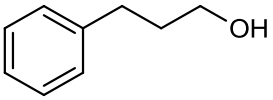
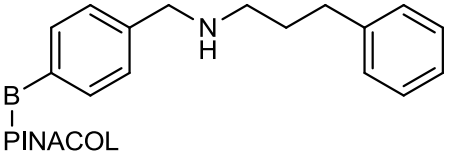
It was pleasing to discover that the para- and meta-boronic ester alcohols react with several primary and secondary amines under $[Ru(p\text{-cymene})Cl_2]_2$/DPEphos/$Na_2CO_3$ conditions were successful. In order to show the general applicability of this method for the N-alkylation of amine with alcohol, it was decided to use boronic ester amine to react with some primary alcohols following the same procedure. All results are shown below (Scheme 2.27 and 2.28, Table 2.21 and 2.22).



2.46

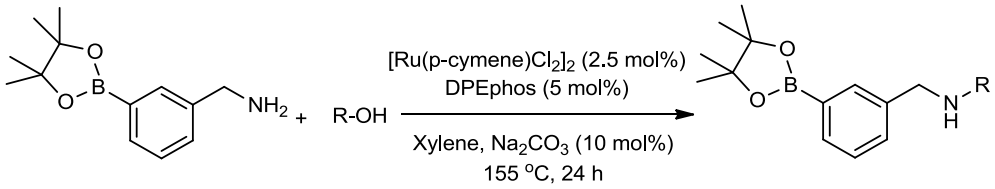
Scheme 2.27. *Para-boronic amine reaction with alcohol*.

Entry	**Starting alcohol**		**Product**	**Isolated yield (%)[a]**
1		2.47		60

2		2.48		61
3		2.49		64

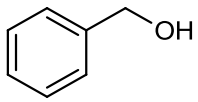
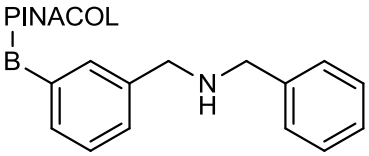
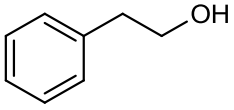
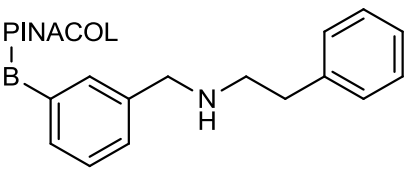
[a] Reactions carried out on 1 mmol in xylene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

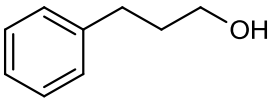
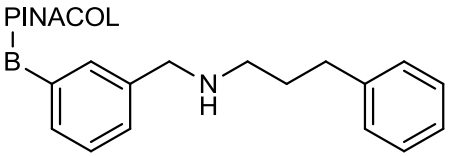
Table 2.21. *Variation of alcohols with para-boronic amines*.



2.50

Scheme 2.28. *Meta-boronic amine reaction with alcohol*.

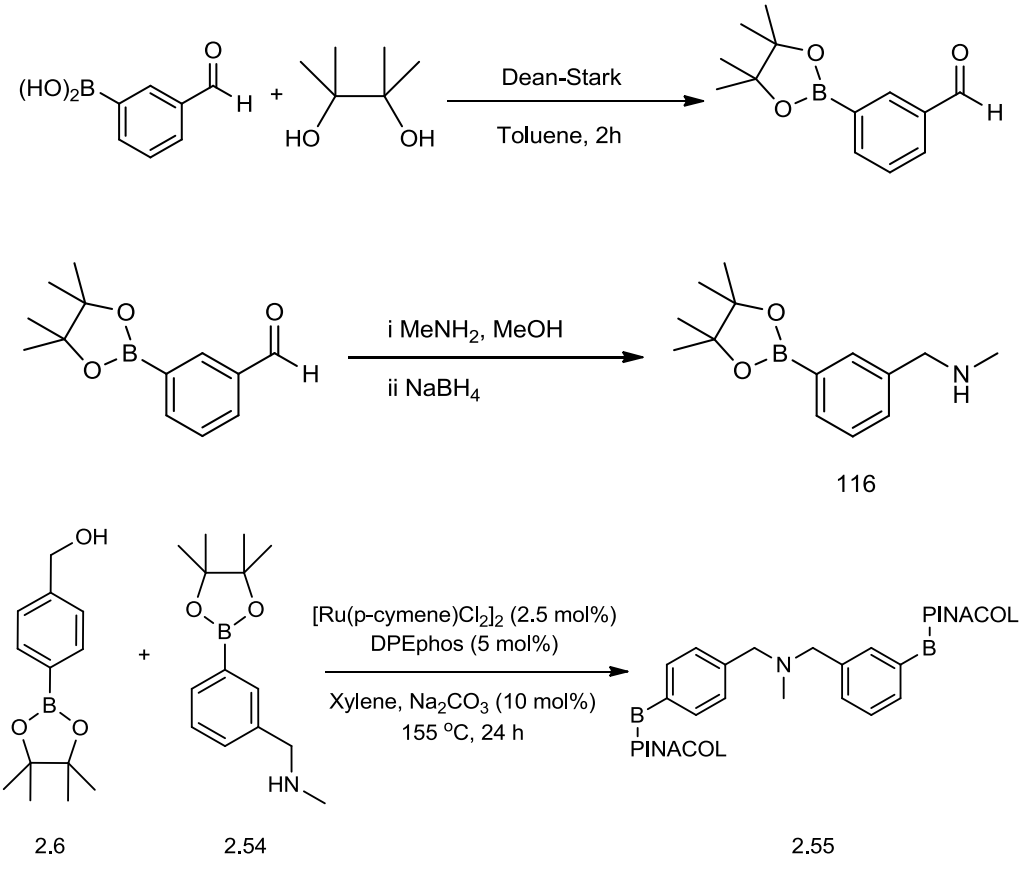
Entry	**Starting alcohol**		**Product**	**Isolated yield (%)[a]**
1		2.51		61
2		2.52		53

3		2.53		60

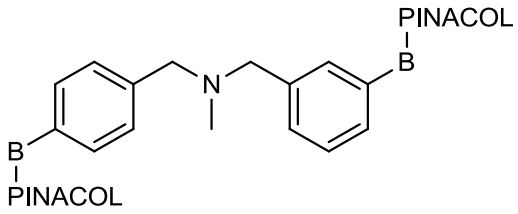
[a] Reactions carried out on 1 mmol in xylene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

Table 2.22. *Variation of alcohols with meta-boronic amines*.

On the basis of these results, the N-alkylation of boronic amines with alcohol under the $[Ru(p\text{-cymene})Cl_2]_2$/DPEphos/$Na_2CO_3$ conditions was found to be suitable for primary boronic ester amines by borrowing hydrogen methodology. However, the isolated yield of these reactions seemed to be lower than when boronic ester alcohols react with amines. This was possibly due to the lone pair electrons on the boronic ester amines were less active than normal amines. In the final part, we chose para-boronic ester alcohol **2.6** to react with meta-boronic ester amines **2.54** to form a compound **2.55** which contains two boron atoms (Scheme 2.29, Table 2.23).



Scheme 2.29. *Meta-boronic amine reaction with para-boronic alcohol*.

Entry		Product	Isolated yield (%)[a]
1	2.55		82

[a] Reactions carried out on 1 mmol in xylene (1 mL), alcohol:amine (1:1); Conversions are based on boronic ester and are determined by ^{1}H NMR analysis.

Table 2.23. *Para-boronic ester alcohol with meta-boronic ester amines.*

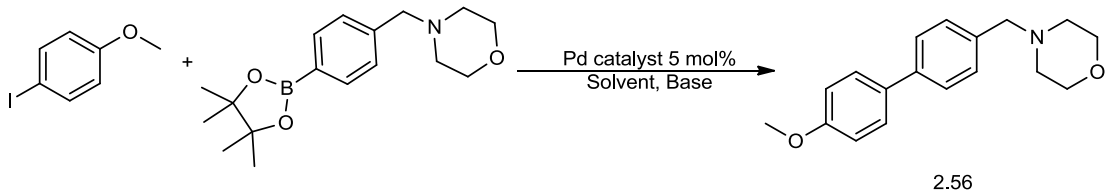
In summary, the [Ru(p-cymene)Cl_2]$_2$/DPEphos/Na_2CO_3 conditions were found to be highly efficient for the N-alkylation of boronic ester alcohols with primary and secondary amines and the boronic ester amines with phenethyl alcohol using a borrowing hydrogen strategy. It was discovered that the [Ru(p-cymene)Cl_2]$_2$/ DPEphos/Na_2CO_3 combination was best suited for this transformation *via* borrowing hydrogen and optimisation of the reaction was also carried out. Hence, a number of primary amines and alcohols were converted into the corresponding secondary amines in good yield by refluxing the alcohol and amine in the presence of 2.5 mol% of [Ru(*p*-cymene)Cl_2]$_2$, 5 mol% DPEphos and Na_2CO_3 at xylene for 24 hours.

Additionally, there are several advantages to use this new synthetic route rather than the previous reductive amination route: (1) alcohols are relatively inexpensive and more readily available than the corresponding halides or carbonyl compounds, (2) a low loading of catalyst is needed in the reaction and the selectivity of the reaction can be controlled with the catalyst, (3) water is the only by-product avoiding the production of wasteful or toxic products, (4) equimolar amounts of starting material used in the reaction means that all of the atoms of the reactants are incorporated. Moreover, this "borrowing hydrogen" methodology is potentially attractive to pharmaceuticals and industry. This methodology has been applied to the synthesis of some simply pharmaceutical drugs by Williams group[41] and can be further

developed in the future. Tony also reported that the potential for formation of strong complexes between hydroxyl containing therapeutic agents and boronic-acid terminated poly(lactide) suggests a versatile and highly specific route to quantitative polymer-drug conjugates and nanoconjugates, which have become a key target as drug delivery vehicles.[96] In the future, we may use this "borrowing hydrogen" methodology to create a host of potential sensing and drug delivery applications.

2.5 One Pot Reaction – Borrowing Hydrogen and Suzuki reaction

The Suzuki reaction is one of the most famous organic reactions in the world and was first reported by Akira Suzuki and co-workers in 1979. The 2010 Nobel Prize in Chemistry was awarded in part to Suzuki for his discovery and development of this reaction. The Suzuki cross coupling reaction is an extremely versatile methodology for generation of carbon-carbon bonds. Moreover, my research has investigated the use of alcohols as alkylating agent for the formation of new C-C and C-N bonds. Intrigued by how efficient this could be if we blended the Borrowing hydrogen reaction with the Suzuki reaction, we undertook several optimisation steps, which are all summarised below.



2.56

Scheme 2.30. Suzuki reaction.

Entry	catalysts	Base	Solvent	Temperature (^oC)	Conversion into 2.56 (%)[a]
1	$PdCl_2$(DPPf)	K_2CO_3	PhMe	115	46

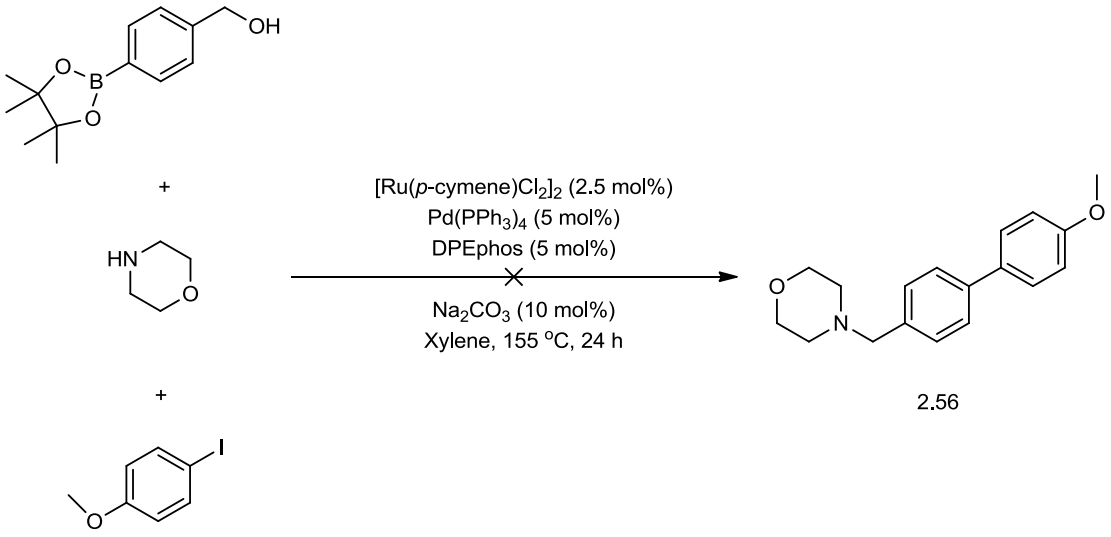
2	$Pd(PPh_3)_4$	K_2CO_3	PhMe	115	52
3	$Pd(OAc)_2$	K_2CO_3	PhMe	115	33
4	$PdCl_2(DPPf)$	Na_2CO_3	PhMe	115	46
5	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	115	74
6	$Pd(OAc)_2$	Na_2CO_3	PhMe	115	30
7	$PdCl_2(DPPf)$	K_2CO_3	Dimethoxyethane	100	41
8	$Pd(PPh_3)_4$	K_2CO_3	Dimethoxyethane	100	38
9	$Pd(OAc)_2$	K_2CO_3	Dimethoxyethane	100	16
10	$PdCl_2(DPPf)$	Na_2CO_3	Dimethoxyethane	100	55
11	$Pd(PPh_3)_4$	Na_2CO_3	Dimethoxyethane	100	69
12	$Pd(OAc)_2$	Na_2CO_3	Dimethoxyethane	100	53
13	$PdCl_2(DPPf)$	K_2CO_3	*p*-xylene	155	29
14	$Pd(PPh_3)_4$	K_2CO_3	*p*-xylene	155	32
15	$Pd(OAc)_2$	K_2CO_3	*p*-xylene	155	11
16	$PdCl_2(DPPf)$	Na_2CO_3	*p*-xylene	155	67
17	$Pd(PPh_3)_4$	Na_2CO_3	*p*-xylene	155	90
18	$Pd(OAc)_2$	Na_2CO_3	*p*-xylene	155	51

[a] Conversions are based on boronic acid and are determined by ^1H NMR analysis.

Conditions: Boronic ester (0.3032g, 1mmol), 4-iodoanisole (0.234g, 1mmol), solvent (2 ml), base (10 mol%), 20 h.

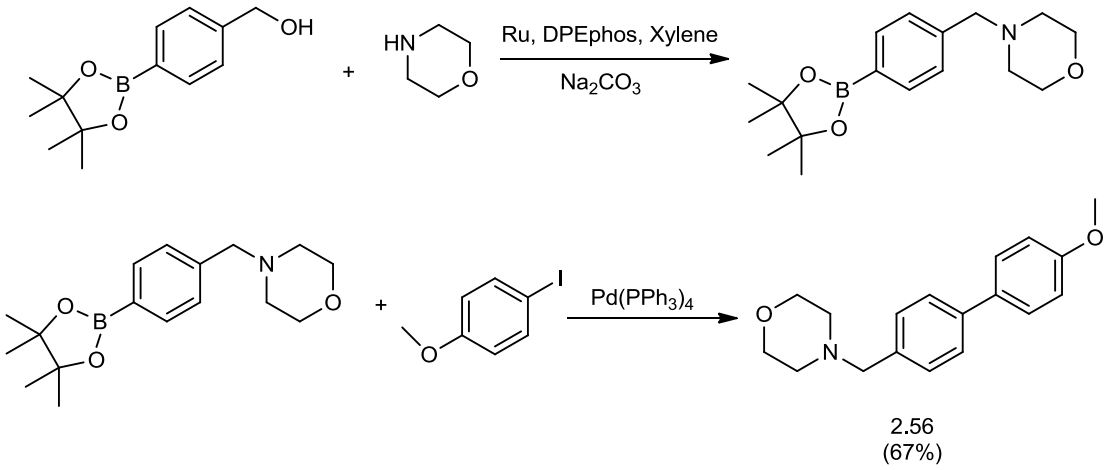
Table 2.24. *Reaction conditions screem.*

On the basis of above results, we then turned our attention to the one-pot "borrowing hydrogen-suzuki reaction". Our investigation started with the reaction of boronic alcohol, morpholine and methoxybenzene mixed together with $Pd(PPh_3)_4$, $[Ru(p\text{-cymene})Cl_2]_2$, DPEphos and Na_2CO_3 in *p*-xylene. The reaction was not found to be successful (Scheme 2.31).



Scheme 2.31. *"One-pot" reaction.*

The major components observed were three starting materials. It may be caused by the palladium and ruthenium catalysts which were inhibited each other. Afterwards, the best conditions we found for our reaction were to finish the "borrowing hydrogen" first, and then add the 4-iodoanisole and Pd catalysts directly into the reaction without any purification. We then turned our attention to the "one pot" reaction obtaining the product in 67% yield (Scheme 2.32).



Scheme 2.32. "*One pot" reaction.*

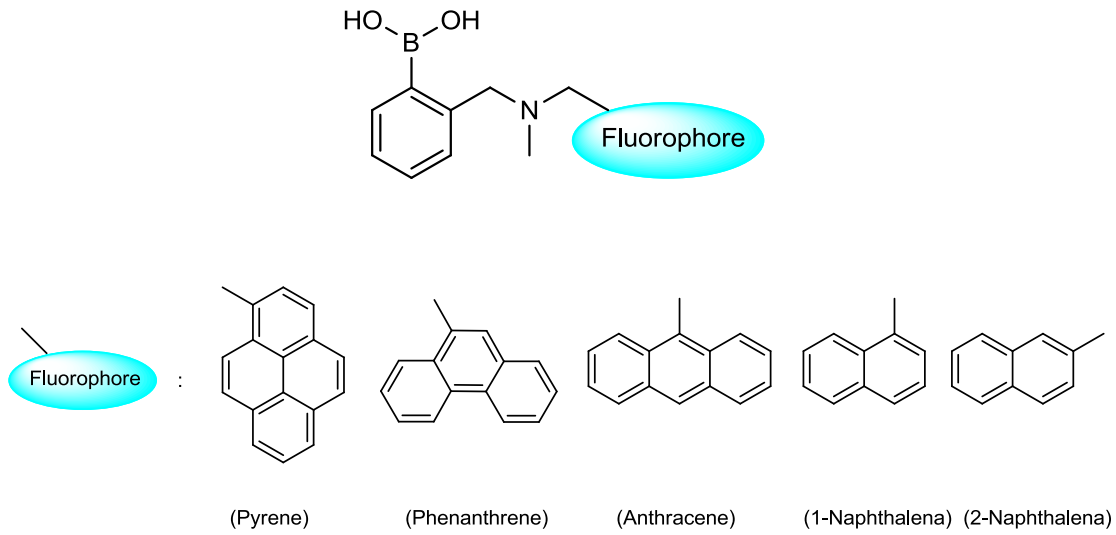
In summary, this one pot reaction has been shown to be successful by using these conditions. In the future, we can use the same conditions to form more complex compounds in short reaction period.

3. Results and Discussion II – Boronic Acid Sensors

3.1 Aims

At the heart of the last chemistry discussed is the temporary activation of an alcohol by oxidation to a carbonyl compound by a process that we have termed “borrowing hydrogen”. The next step, of this research will be applied to the synthesis of a range of boronic acid molecular sensors, providing an alternative to the traditional methods which use mutagenic alkyl halides as the alkylating agents. In the first instance, these will be applied to the preparation of known sensor molecules, used for detecting saccharides.

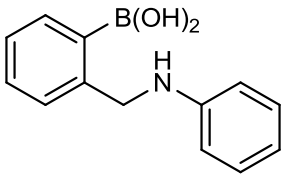
There are several fluorophores which are all commercially available as their aldehyde derivatives. They are comparatively inexpensive and have similar photophysical properties.



Scheme 3.1. *Boronic acid sensors with variable fluorophore units*.

3.2 Background

The use of boronic acid fluorescent sensors for saccharide detection is a relatively new field. Czarnik published the first report in 1992[60] and D-Glucose selectivity was achieved two years later in 1994 by Shinkai and James.[61] There are two major distinct design principles for a diverse range of boronic acid base fluorescent sensors in the scientific literature: internal charge transfer (ICT) and photoinduced electron transfer (PET). In 1995, the first concerted effort to couple donor and acceptor fragments to produce an ICT sensor for saccharides was designed by Sandanayake.[97] Subsequent redesign of aniline based sensor **3.1** baseed on ICT concepts can be used for saccharide sensing.[60d] It is very important to point out that for an ICT sensor they do not only change the fluorescence intensity but also undergo a shift of the fluorescent emission wavelength when it binds with saccharides (Figure 3.1).[98]



3.1

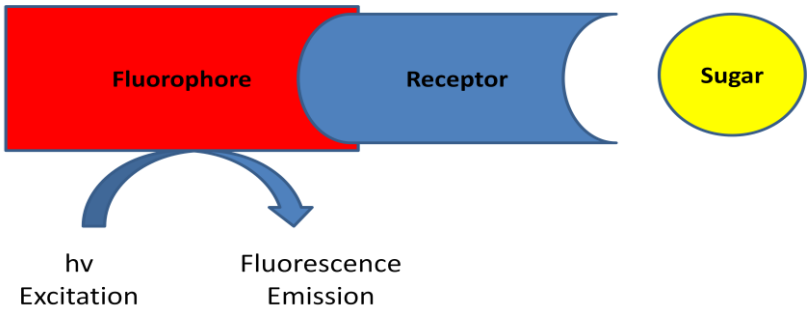
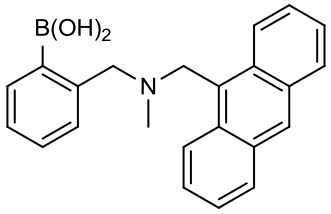


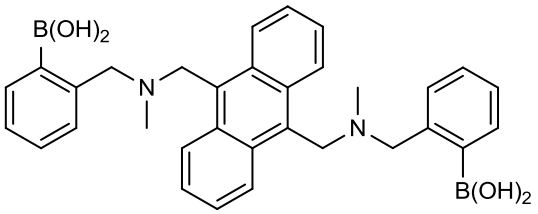
Figure 3.1. *Schematic representation of the overlapped fluorophore-receptor design assembly for fluorescent internal charge transfer (ICT) sensory systems.*

The first fluorescence PET sensor (anthracene based *N*-methyl-*o*-(aminomethyl)

phenylboronic acid **3.2**) was reported by James in 1994.[99] The addition of saccharides can increase the fluorescent intensity of compound **3.2,** and then compound **3.3** was prepared and is selective for D-glucose. Subsequently, the synthesis of novel fluorescent PET sensors has become a most significant research in the James research group.

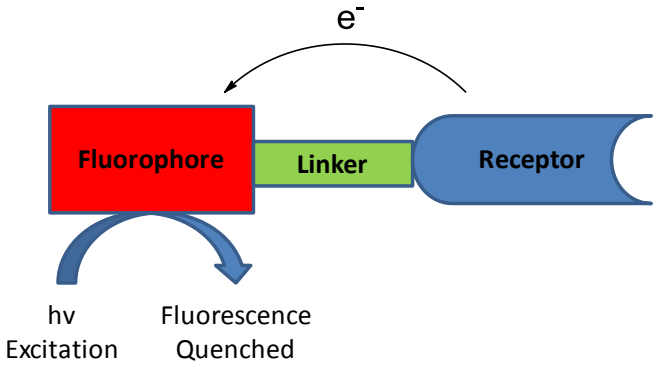


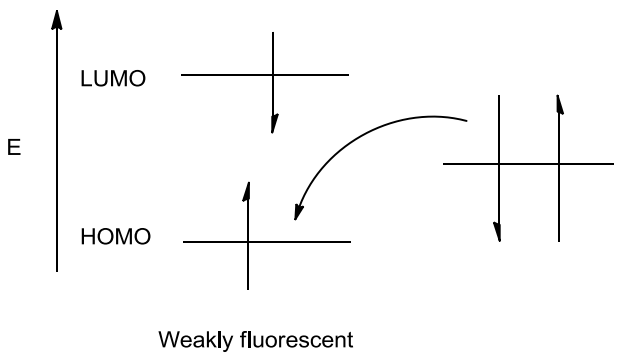
3.2



3.3

The fluorescence "off-on" mechanism of the PET sensor can be clearly described in Figure 3.2.





Weakly fluorescent

The lone pair electrons on nitrogen undergo internal transfer to the fluorophore before boronic acid binds with sugar, which can cause fluorescence quenching.

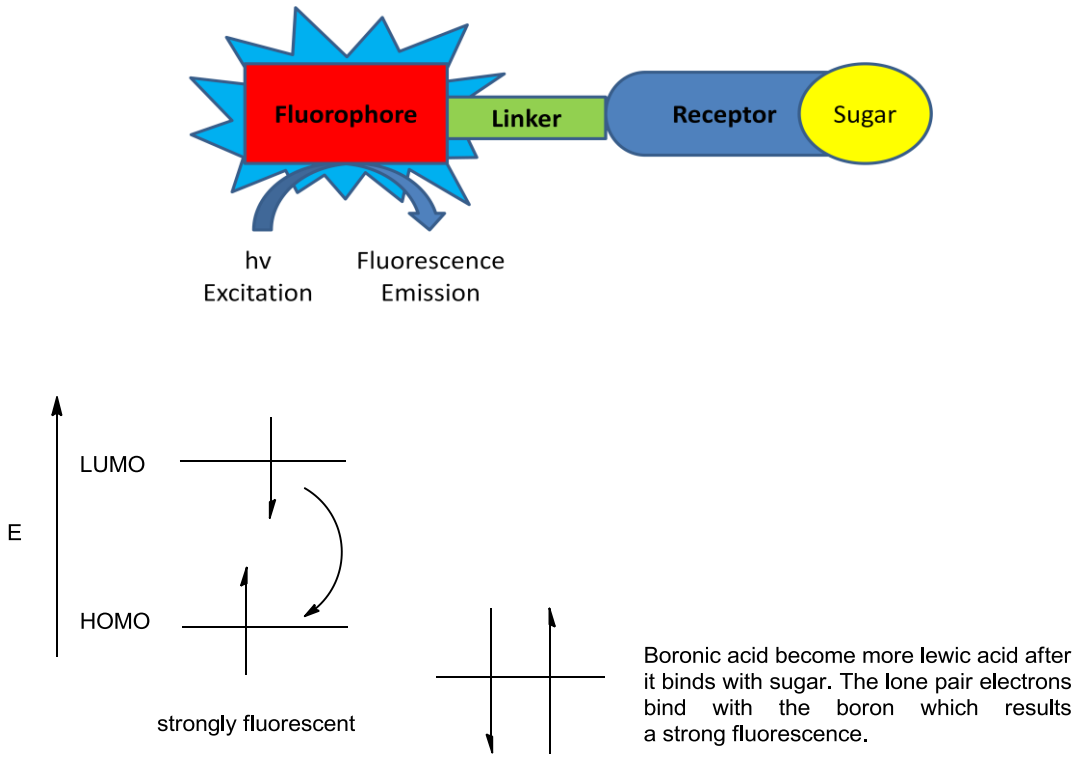
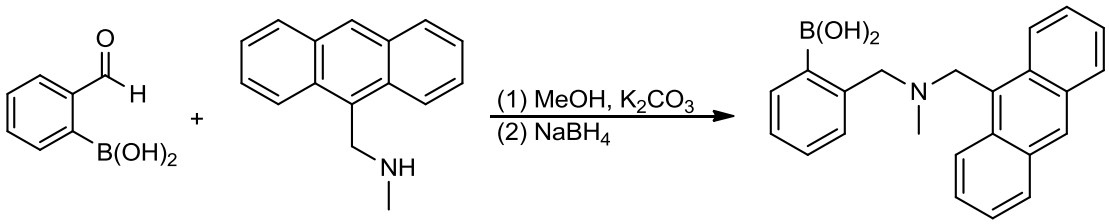


Figure 3.2. *Schematic representation of the fluorophore-spacer-receptor design assembly for fluorescence Pet sensory system.*

In the neutral boronic acid state, one of the electrons electron occupying the highest occupied molecular orbital (HOMO) of the fluorophore can be promoted to the lowest unoccupied molecular orbital (LUMO) by absorbing energy. The energy of lone pair electrons on nitrogen is just higher than HOMO in the fluorophore, one of electrons will transfer to the HOMO of the fluorophore, which will quench the emission transition of the electron on LUMO to HOMO. After the boronic acid binds with a saccharide, the so-formed boronate becames more Lewis acidic and the lone pair electrons bind strongly with the boron atom. The energy of lone pair electrons on nitrogen is lower than HOMO in the fluorophore, resulting in a strong fluorescence.[100]

3.3 Initial Work

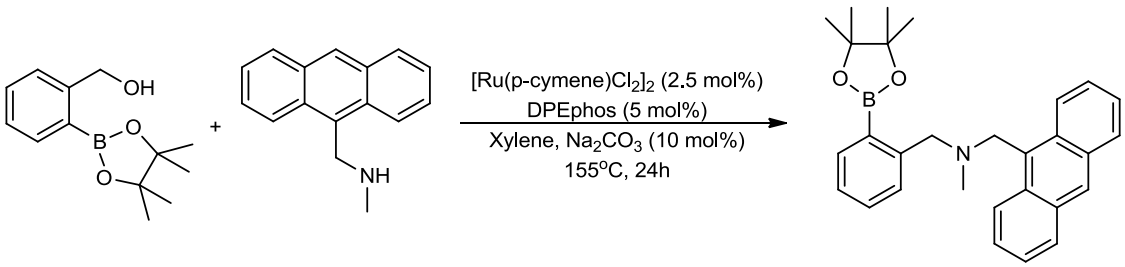
Anthracene is a common fluorophore and widely used in the fluorescent sensing field. In the initial studies, the reaction of boronic acid **3.4** and anthracene was used to form monoboronic acid sensor **3.2**(Scheme 3.2).[101] The unprotected sensor **3.2** was prepared for comparison using a standard reductive amination procedure in 54% yield.



3.4 3.2

Scheme 3.2. *Reaction of boronic acid and anthracene.*

We decided to compare the difference between the boronic acid sensors with and without pinacol protected boron. So we synthesised a pinacol protected monoboronic acid sensor **3.5** by using the borrowing hydrogen method (Scheme 3.3).



3.5

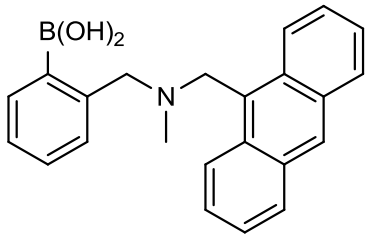
Scheme 3.3. *Reaction of boronic acid ester and anthracene.*

We used the strategy to prepare this known saccharide sensor 3.5 in 84% yield. The

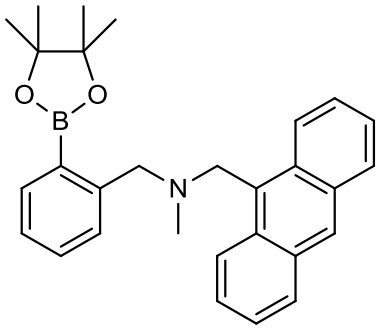
success of this reaction is probably due to the use of the less sterically demanding methyl substituted secondary amine.[102]

3.4 Results and discussion

The fluorescence titrations of the monoboronic acid compounds **3.2** and **3.5** with D-glucose, D-fructose, D-galactose and D-mannose were carried out in an aqueous methanolic buffer solution (52.1 wt% methanol at pH 8.21 (KCl, 0.01 mol/L; KH_2PO_4, 0.00275 mol/L; Na_2HPO_4, 0.00276 mol/L)).[56a]



3.2



3.5

added sugar (g)	mol/L	Time (mins)
0	0	0
0.005	2.78×10^{-4}	5
0.01	5.56×10^{-4}	10
0.02	1.11×10^{-3}	15
0.04	2.22×10^{-3}	20
0.06	3.33×10^{-3}	25
0.1	5.56×10^{-3}	30
0.15	8.33×10^{-3}	35
0.2	1.11×10^{-2}	40
0.3	1.67×10^{-2}	45
0.4	2.22×10^{-2}	50
0.6	3.33×10^{-2}	55
0.8	4.44×10^{-2}	60
1.2	6.67×10^{-2}	65
2	0.11	70

3	0.17	75
5	0.28	80
7	0.39	85

Table 3.1. Effect of increasing *saccharide concentration.*

The sensor was added to a 100 mL volumetric flask and then was made up to the required volume with HPLC grade methanol to generate a stock solution of know molarities. The stock solution was transferred *via* micro-syringe to a flask which contained the pH 8.21 aqueous methanolic buffer (the buffer solution was strred). The fluorescence intensity of the monoboronic acid sensors **3.2** and **3.5** increased with increasing saccharide concentration. We increased the saccharide concentration every 5 minutes (Table **3.1**). The observed stability constants (K_{obs}) of PET sensors **3.2** and **3.5** were calculated by the fitting of emission intensity *vs.* saccharide concentration curves.[103] The emission wavelengths used for each fluorophore in determining the emission intensity are in Table **3.2**. The observed stability constants (K_{obs}) calculated is reported in Table **3.3** and **3.4**, and fluorescence intensity *vs*. saccharide concentration is detailed in graph **1-8**. Identical fluorescence behaviour of the two sensors with added saccharide was observed (the protecting group is displaced under the measurement conditions) and clearly demonstrates the validity of our new synthetic procedure in the preparation of fluorescence sensors for saccharides. We are currently exploring the use of our procedure in the preparation of novel imprinted material based sensors.[102]

Fluorophore	**Concentration/mol dm^{-3}**	**λ_{ex}/nm**	**λ_{em}/nm**
Anthracene	1.0 × 10-6	367	413

Table 3.2. *Fluorescence measurement conditions*

Sensor	D-Glucose		D-Fructose	
	K_{obs}/dm^3 Mol^{-1}	Fluorescence enhancement	K_{obs}/dm^3 Mol^{-1}	Fluorescence enhancement
3.2	87 ± 8	3.0	528 ± 27	3.0
3.5	87 ± 9	3.0	613 ± 26	3.3

Table 3.3. *K_{obs} and fluorescence enhancements for sensors 119 and 120.*

Sensor	D-Galactose		D-Mannose	
	K_{obs}/dm^3 Mol^{-1}	Fluorescence enhancement	K_{obs}/dm^3 Mol^{-1}	Fluorescence enhancement
3.2	98 ± 6	3.1	216 ± 37	3.0
3.5	102 ± 6	3.0	130 ± 17	3.3

Table 3.4. *K_{obs} and fluorescence enhancements for sensors 3.2 and 3.5.*

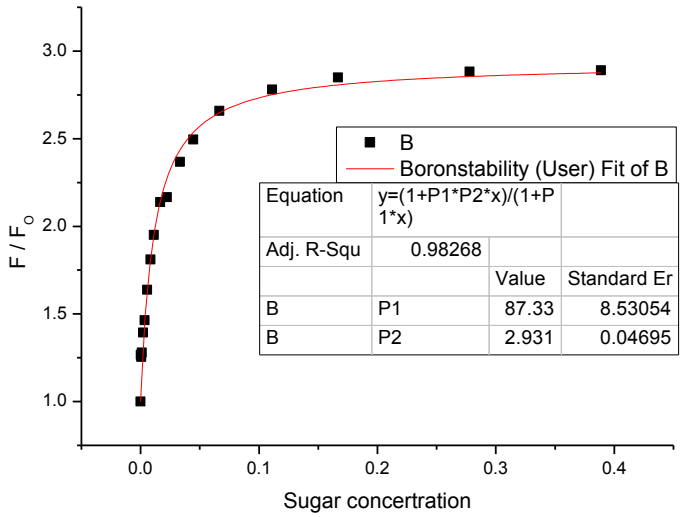
Monoboronic acid sensor 3.2 fluorescent

F = fluorescent intensity (sugar added); F_o = fluorescent intensity (no sugar added);

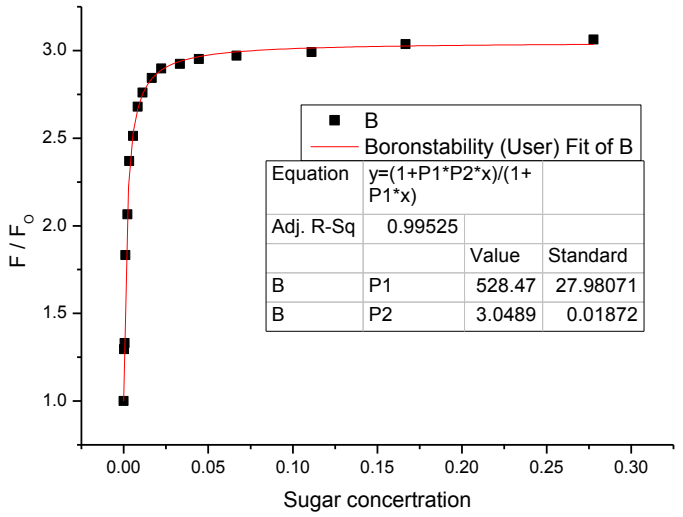
$P_1 = K_{obs}$ (sugar binding constant); $P_2 = F / F_o$;

X = sugar concentration (mol/L);

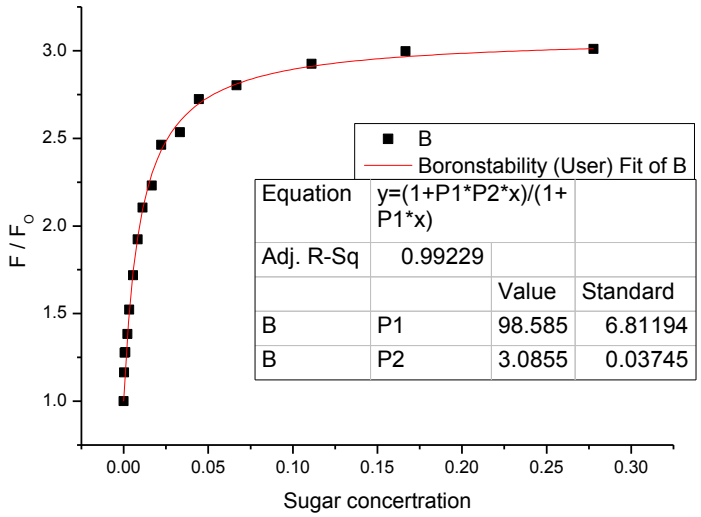
1. D-glucose



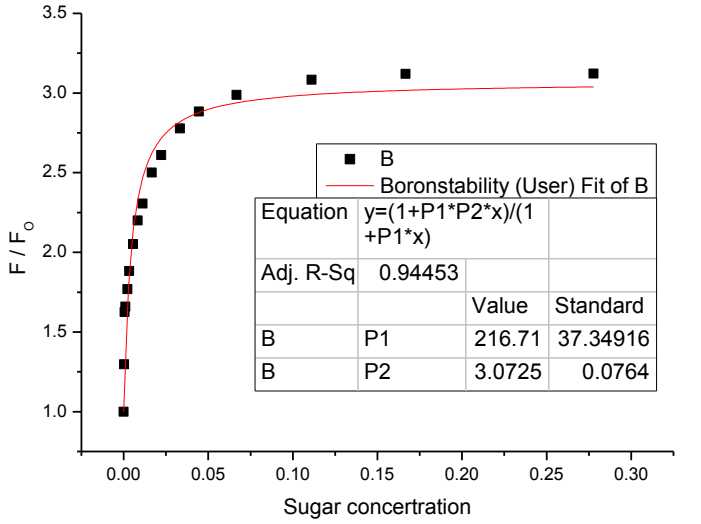
2. D-fructose



3. D-galactose



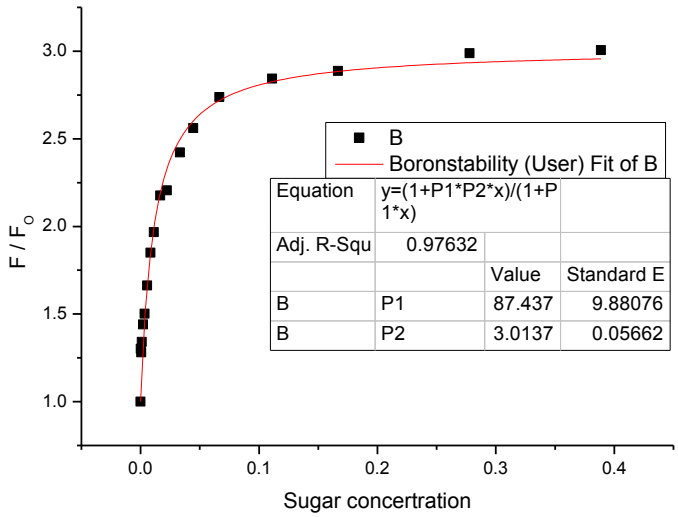
4. D-mannose



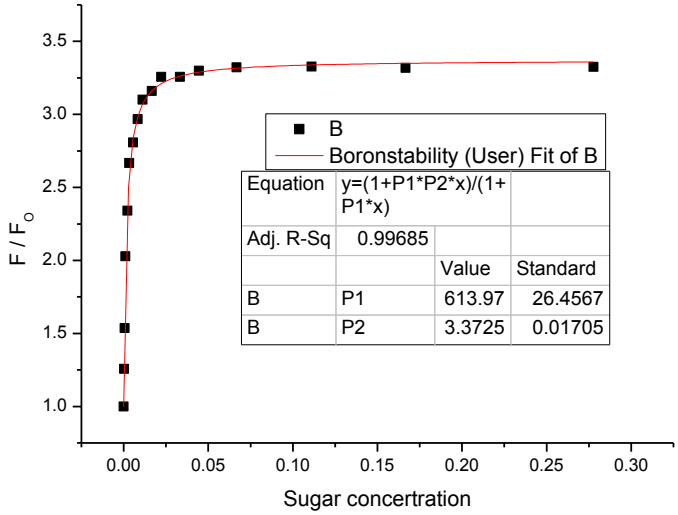
Graph 1-4. *Relative fluorescence intensity vs. saccharide concentration profile of sensor 3.2*.

Monoboronic acid sensor 3.5 fluorescent

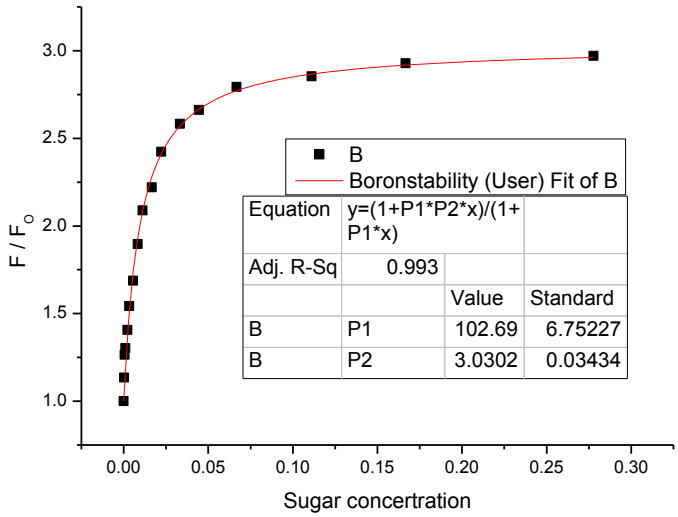
5. D-glucose



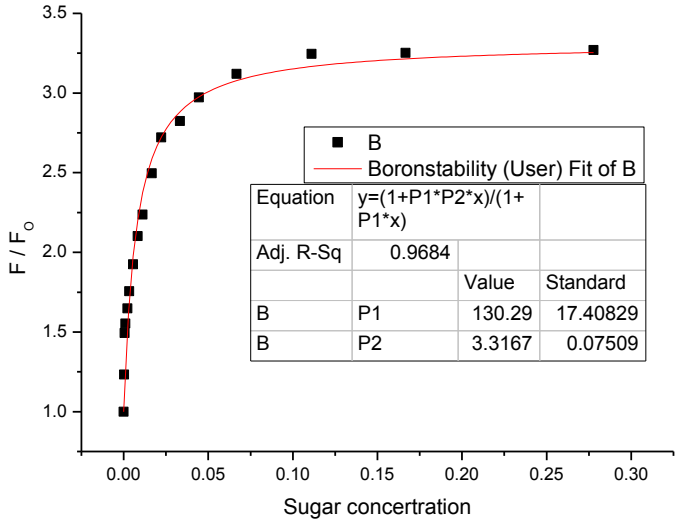
6. D-fructose



7. D-galactose



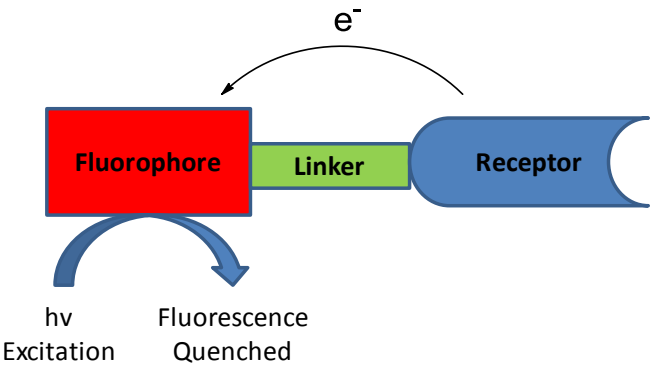
8. D-mannose

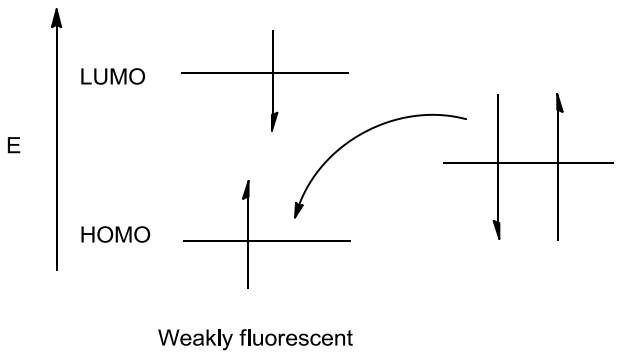


Graph 5-8. *Relative fluorescence intensity vs. saccharide concentration profile of sensor 3.5*.

In summary, comparing sensors **3.2** and **3.5**, the stability constants and fluorescent enhancements are similar, which indicates that the pinacol group does not significantly influence the sugar binding. There are two advantages to the use of this methodology: (1) this methodology is relatively simple to synthetise boronic acid sensors; (2) the fluorescence was not affected by any transition metal ions. If there were some transition metal left in the reaction, these transition metal ions can be

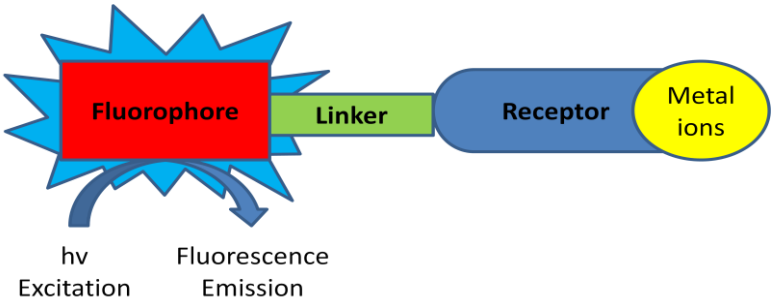
detected by fluorescence and there could be some observable change in the fluorescence emission. The boronic acid sensor which we made was a classical photoinduced electron transfer (PET). For free PET, the electron occupying on the highest occupied molecular orbital (HOMO) of the fluorophore can be promoted to the lowest unoccupied molecular orbital (LUMO) by absorbing energy. The energy of lone pair electrons on nitrogen is just higher than HOMO in the fluorophore, so one of electron will transfer to the HOMO of the fluorophore, which quench the emission transition of the electron on LUMO to HOMO. Transition metal ions can also interact with boron. Which could result in the boron becoming more Lewis acidic and the lone pair of electrons could bind with the boron atom more strongly. The energy of the lone pair of electrons on nitrogen is lower than the HOMO in the fluorophore, which may result in an increase in fluorescence.[100] However, this situation did not happen in our fluorescence experiments which means there was not any transition metal left in the system. In future, we can use the borrowing hydrogen method to synthesize more fluorescent sensors in a much easier fashion.

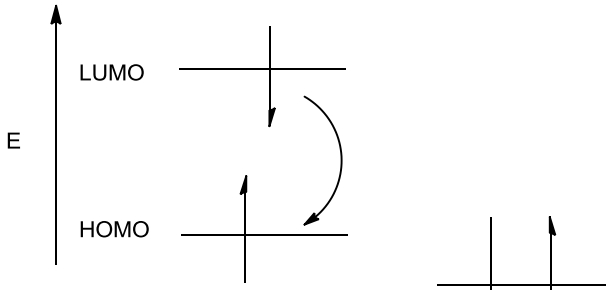




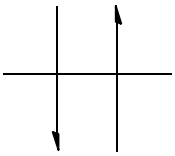
Weakly fluorescent

The lone pair electrons on nitrogen undergo internal transfer to the fluorophore before boronic acid binds with metal ions, which can cause fluorescence quenching.





strongly fluorescent



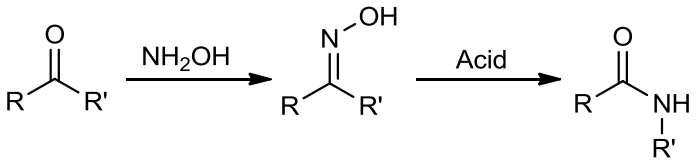
Boronic acid become more lewic acid after it binds with metal ions. The lone pair electrons are turning to bind with the boron which result a strong fluorescence.

4. Results and Discussion III – Amides from Oximes

4.1 Aims

Oximes are chemical compounds belonging to the imine family and they have been used as analytical reagents since the beginning of the 20th century.[63, 104] Oximes and their derivatives are widely used in the synthesis of different nitrogen containing acyclic and heterocyclic compounds. Oximes have found extensive application within organic synthesis and they are employed in a diverse range of reactions.[105] The oxime function can be easily introduced into an organic molecule, which involves oximation of a carbonyl group with hydroxylamine, reduction of nitro compounds, oxidation of amines, oxidative ammonolysis, nitrosation of hydrocarbons, *etc*. Moreover, oximes can be used as protecting groups in carbonyl chemistry and can also be used to purify and characterise carbonyl compounds, specifically ketones and aldehydes.[106]

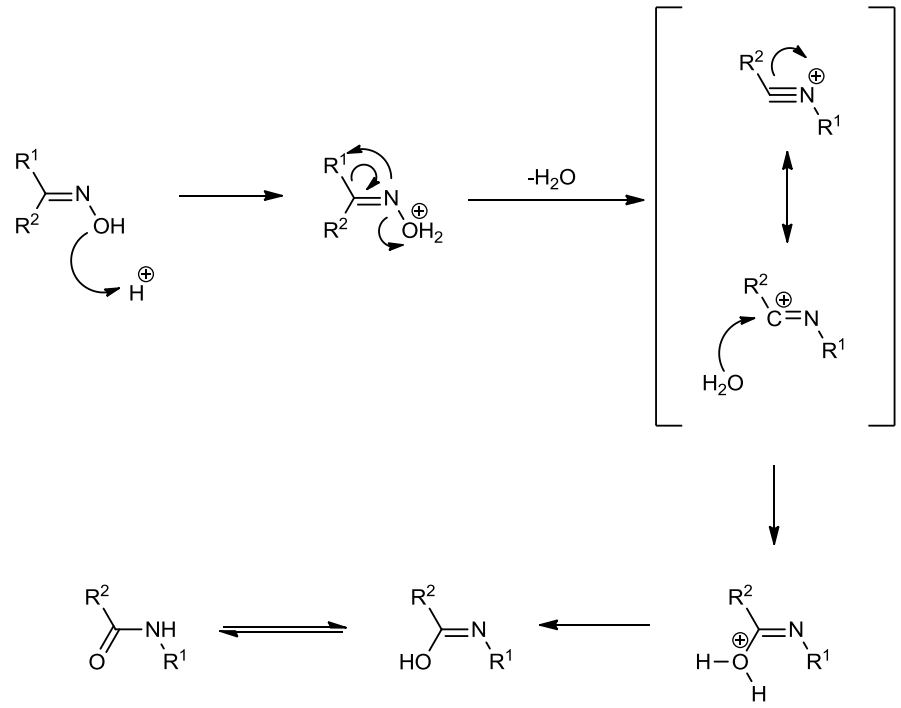
Oximes can be prepared by the condensation of a ketone or an aldehyde with hydroxylamine and these reactions are typically run at room temperature in an alcoholic solvent in the presence of a base. Ketones react with hydroxylamine to form ketoximes and aldoximes are synthesised by the reaction of aldehydes with hydroxylamine. Oximes can be changed to the corresponding amide derivatives. Amide bond formation by using metal catalysts is now well known in the area of aldoxime rearrangement into a primary amide and the Beckmann rearrangement of ketoximes (Scheme 4.1).



Scheme 4.1. *Beckmann rearrangement.*

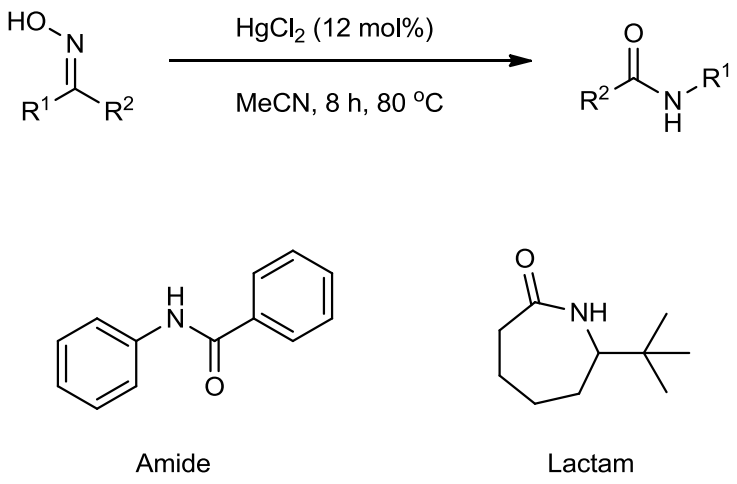
4.2 Background

The Beckmann rearrangement of ketoximes into amides is a useful methodology in organic synthesis. The reaction mechanism of the Beckmann rearrangement is an alkyl migration with expulsion of the hydroxyl group to form a nitrilium ion, the the intermediate is hydrolyzed to form amide (Scheme 4.2).



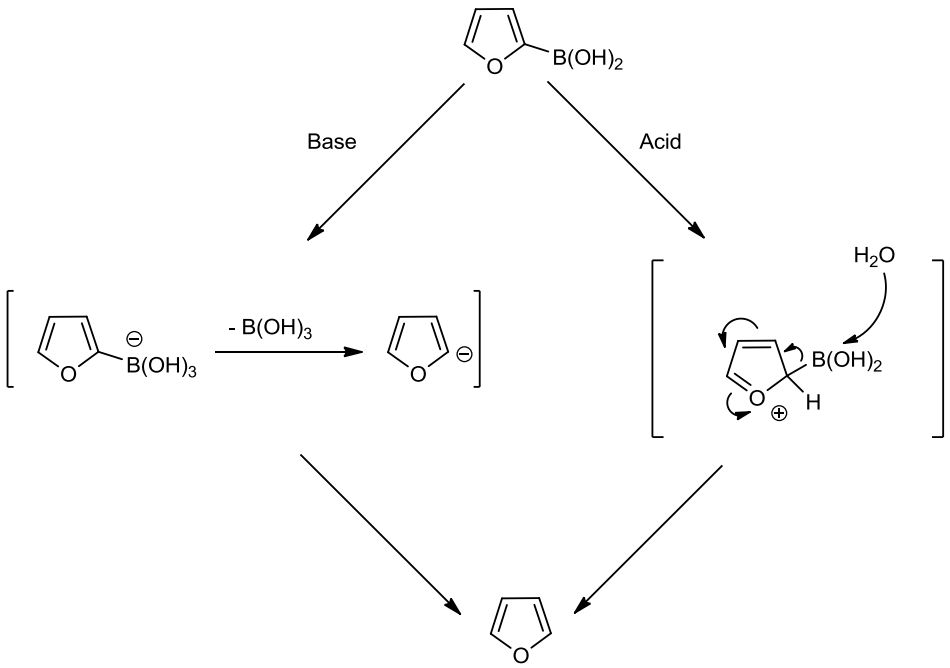
Scheme 4.2. *Beckmann rearrangement.*

However, this reaction requires harsh conditions such as strong acid and high temperature. Although some metal catalysed Beckmann rearrangements have been published, the most attention to the metal catalysed reaction for Beckmann rearrangements was reported by the Park group in 2007. They used acetonitrile as solution and mercury(II) chloride to catalyse a range of ketoximes into their corresponding amides or lactams (Scheme 4.3).[107]



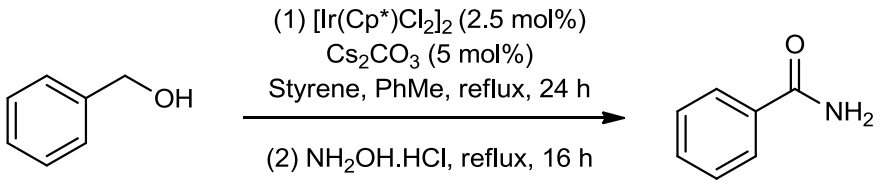
Scheme 4.3. *Mercury catalysed Beckmann rearrangement of ketoximes.*

Most types of boronic acids are highly resistant to protolysis of the C-B bond in neutral aqueous solutions. However, boronic acids are potentially susceptible to acid- or base-catalysed protodeboronation, which is removal of a boronic group. Furan boronic acids are containing electron-withdrawing groups, so a relatively stable carbanion can be formed. Base-catalysed deboronation can become an important unwanted side reaction during palladium-catalysed boronic acid couplings. (Scheme a).[108]



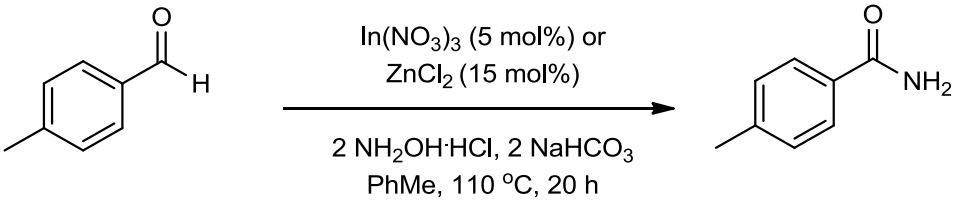
Scheme a. Protodeboronation.

The rearrangement of oximes into amides has been shown to be catalysed by several metal complexes. In 2007, a report by the Williams group demonstrates the potential to start from the alcohol being oxidised into an aldehyde, then condensation with hydroxylamine and subsequent rearrangement to the primary amide (Scheme 4.4).[109]



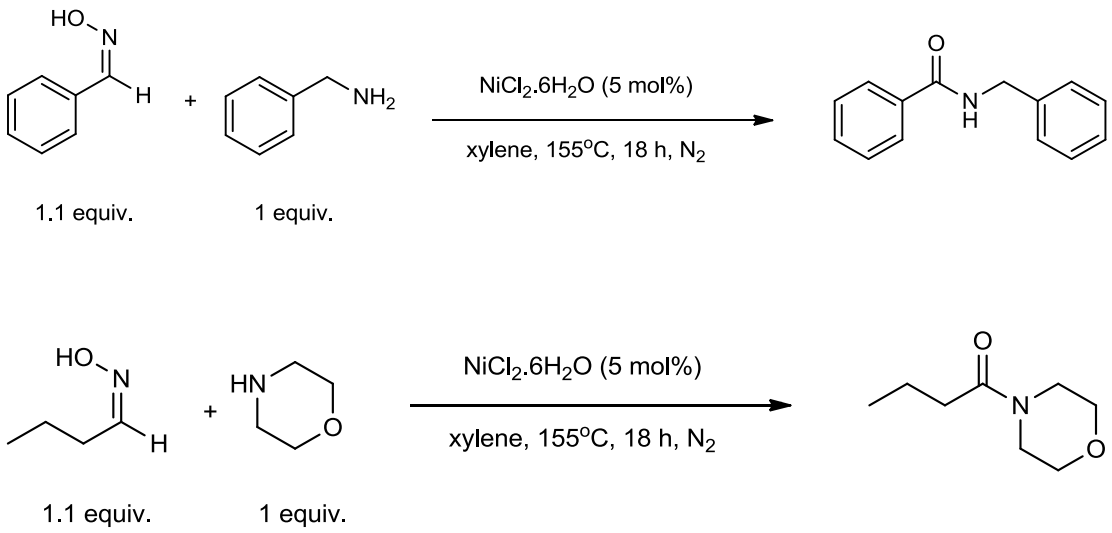
Scheme 4.4. *Alcohol into amide by Iridium catalysts.*

The Williams group has also published a report of indium or zinc salts which have been successfully used as catalysts for the rearrangement of aldehyde (*via oxime*) into primary amides (Scheme 4.5). Zinc salts were new, low-cost and efficient catalysts which rearranged aldoximes into primary amides with good isolated yields.[110]



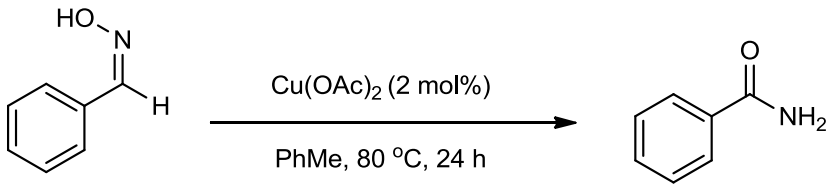
Scheme 4.5. *Aldehyde via oxime into amide.*

An example of secondary or tertiary amide formation was demonstrated by the Williams group in 2010. The simple nickel salt $NiCl_2 \cdot 6H_2O$ catalyses the coupling of aldoximes with amines to give secondary or tertiary amides (Scheme 4.6).[111]



Scheme 4.6. *Secondary and tertiary amides formation.*

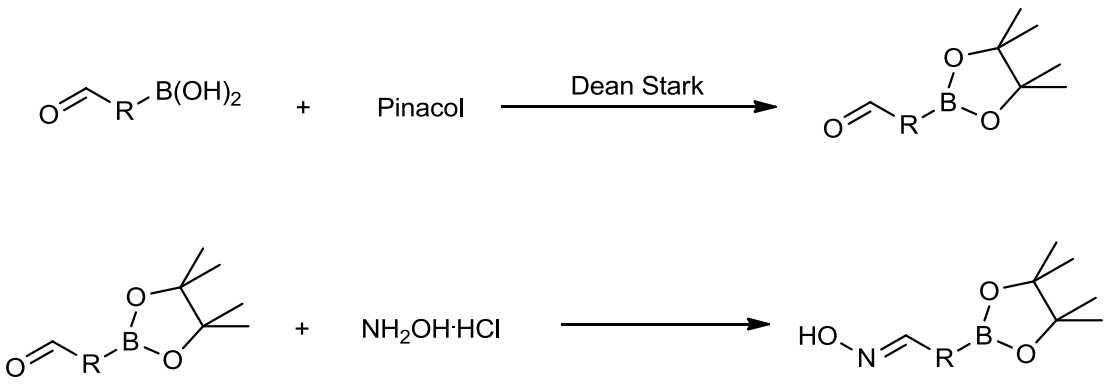
In 2011, the use of homogeneous $Cu(OAc)_2$ was found to be effective for rearrangement of oxime into primary amides by the Williams group (Scheme 4.7).[112]



Scheme 4.7. *Copper-catalyzed rearrangement of oxime into primary amides.*

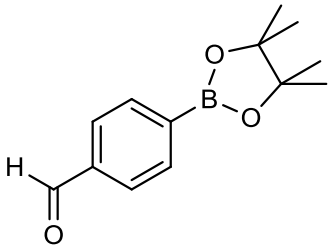
4.3 Initial Work

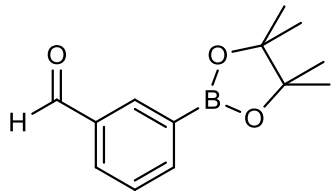
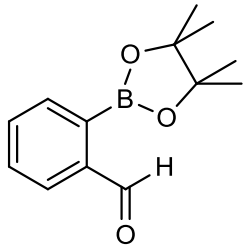
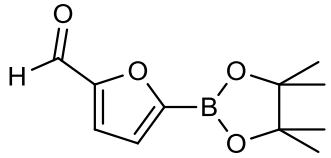
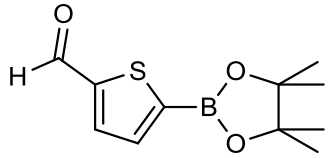
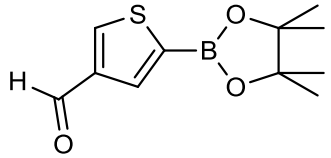
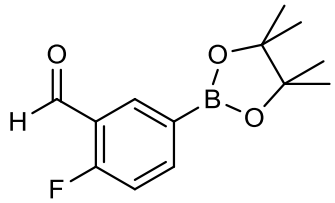
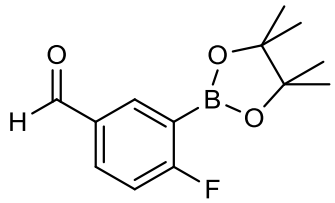
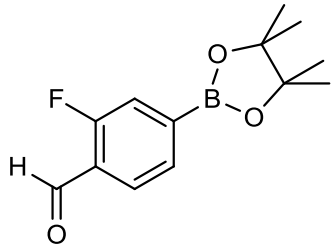
In the initial studies, the reaction of pinacol and different boronic acid aldehydes were used to form boronic esters. As mentioned before, boronic acids are often best handled as their ester derivatives. Afterwards, these boronic esters can be further reacted to give the corresponding boronic aldoximes. Moreover, all of these boronic aldoximes are intended for use in further reactions.



(R = phenyl, furan or thiophene)

Scheme 4.8. *Synthesis of boronic ester and boronic aldoxime.*

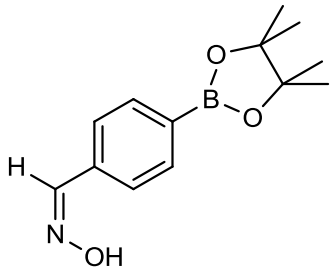
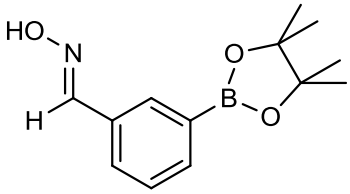
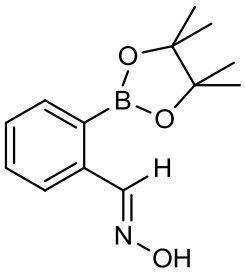
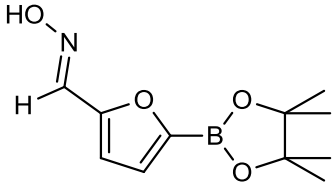
Entry		Boronic ester	Isolated yield (%)
1	**4.1**		94

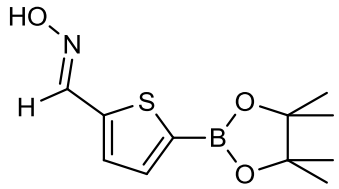
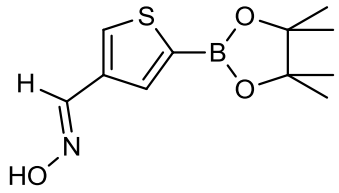
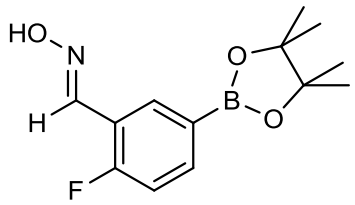
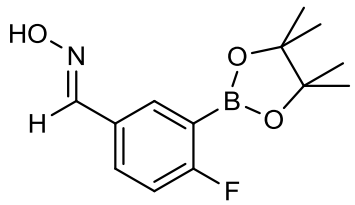
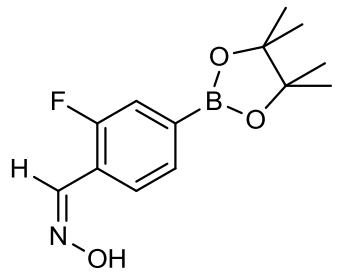
2	**4.2**		90
3	**4.3**		75
4	**4.4**		89
5	**4.5**		90
6	**4.6**		82
7	**4.7**		85
8	**4.8**		84
9	**4.9**		87

Conditions: Boronic aldehyde (20 mmol), pinacol (30 mmol), PhMe (100 mL).

Table 4.1. *Boronic acid esters.*

Fortunately, all boronic ester aldehydes were achieved in excellent isolated yields. We then turned our attention to the scope of next reaction. Aldoximes can be synthesised in a nunber of ways, but the most common method for this reaction is condensation of an aldehyde and hydroxylamine hydrochloride, and then run this reaction under room temperature in an alcoholic solvent such as methanol or ethanol in the presence of base. Several boronic ester aldehydes were converted into the corresponding oximes in good to excellent yields, although one was found to have just 62% yield. It was possible that steric hinderance around the reaction site led to low conversion into oxime being observed (Table 4.2, entry 3).

Entry		Boronic aldoxime	Isolated yield (%)
1	**4.10**		91
2	**4.11**		88
3	**4.12**		62
4	**4.13**		86

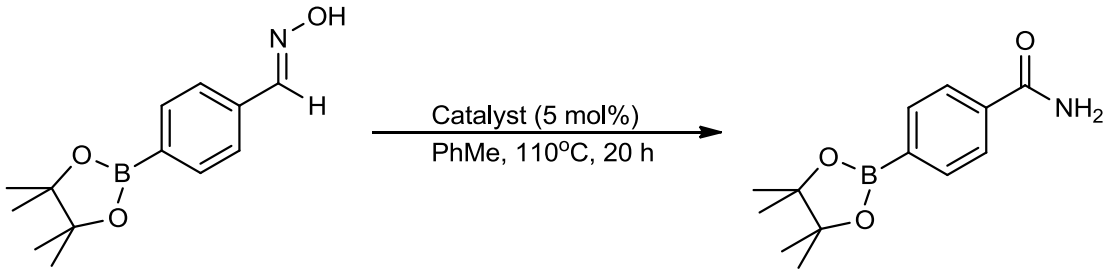
5	**4.14**		82
6	**4.15**		77
7	**4.16**		83
8	**4.17**		80
9	**4.18**		78

Conditions: Boronic aldehyde ester (10 mmol), hydroxylamine hydrochloride salt (20 mmol), NaOAc (30 mmol), EtOH : H_20 (100 mL : 20mL), room temperature, 3 h.

Table 4.2. *Boronic aldoximes.*

4.4 Primary amide formation

The ruthenium, iridium, rhodium and indium catalysts have already been reported well for the rearrangement of aldoximes into a primary amides. However, there is not any report about the rearrangement of a boronic aldoxime into a primary boronic amide. We decided to screen a number of catalysts to find out the best catalyst for this rearrangement (Table 4.3).



4.10 4.19

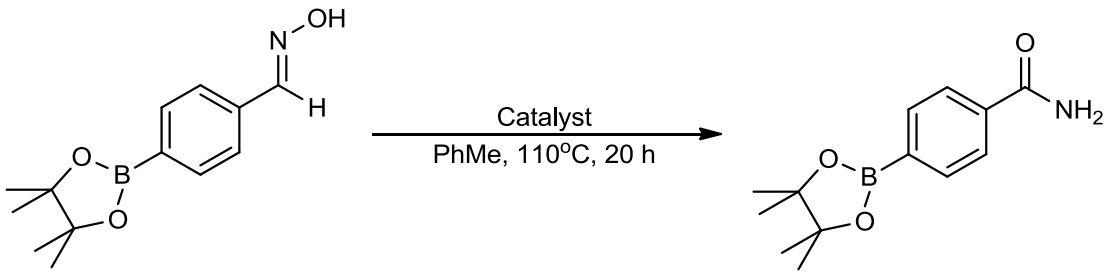
Entry	Catalyst	Conversion into 4.19(%)[a]
1	No catalyst	0
2	$Ca(OH)_2$	10
3	$FeCl_3$	0
4	$In(NO_3)_3{\cdot}H_2O$	12
5	$In(OTf)_3$	18
6	$ZnCl_2$	9
7	$Zn(OTf)_2$	8
8	$InCl_3$	10
9	$Fe(NO_3)_3$	0
10	$Cu(OAc)_2$	95
11	$Pd(OAc)_2$	80

[a] Conversions are based on oxime and are determined by ^{1}H NMR analysis.

Conditions: Boronic aldoxime (0.2471g, 1 mmol), catalyst (5 mol%), PhMe (1 mL), 110 ^{o}C, 20 h.

Table 4.3. *Catalyst screen.*

This initial catalyst screen gave mixed results, but copper acetate stood out as the best potential lead, giving over 90% conversions into boronic amide in 20 hours. Some reactions presented lower and even no conversions which may be caused by boron compounds reacting with metal. Borane complexes can be knew as Lewis acid-base adducts of acidic borane which with basic metal centres resulting in a fourfold co-ordination of the boron atom. This would inhibit the catalyst. Intrigued by how efficient we could make the rearrangement with copper and palladium salts, we examined several different copper and palladium salts to find the lowest catalyst loading and the best catalyst to give high conversion into boronic amide. The set of results obtained is summarised below in Table 4.4.



4.10 4.19

Scheme 4.9. *Synthesis of boronic oxime into amide.*

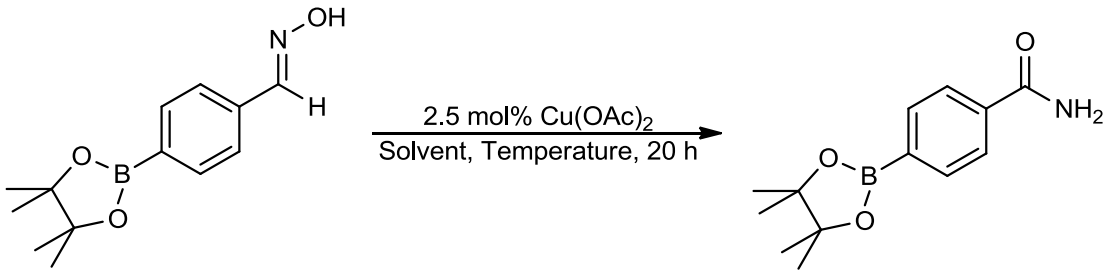
Entry	Catalyst	Catalyst loading (mol%)	Conversion into amide 4.19 (%)[a]
1	$Cu(OAc)_2$	5	95
2	$Cu(OAc)_2$	2.5	94
3	$Cu(OAc)_2$	1	86
4	$Cu(OAc)_2$	0.5	63
5	$CuCl_2$	5	41
6	$CuCl_2$	2.5	22
7	$CuCl_2$	1	10
8	$CuCl_2$	0.5	0

9	$Pd(OAc)_2$	5	80
10	$Pd(OAc)_2$	2.5	77
11	$Pd(OAc)_2$	1	61
12	$Pd(OAc)_2$	0.5	55
13	$PdCl_2$	5	18
14	$PdCl_2$	2.5	10
15	$PdCl_2$	1	0
16	$PdCl_2$	0.5	0

[a] Conversions are based on oxime and are determined by ^1H NMR analysis.

Table 4.4. *Different catalysts screen*

During the course of screening reactions for the conversion of aldoxime into amide (Table 4.4), we found that using 2.5 mol% of $Cu(OAc)_2$ gave 94% conversion after 20 hours which was not very different compared with 5 mol% of $Cu(OAc)_2$. $Pd(OAc)_2$ gave 80% and $CuCl_2$ gave just 41%, whereas $PdCl_2$ did not work to any useful level. We chose copper acetate as our catalyst to continue optimisation studies. In the next step, we determined the best solvent for this reaction using 2.5 mol% copper acetate as catalyst.



4.10 4.19

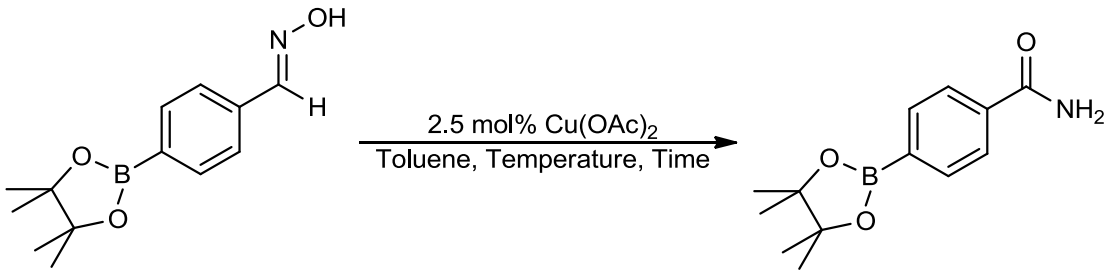
Entry	Solvent	Temperature (^oC)	Conversion into 4.19 (%)[a]
1	Xylene	155	94
2	Toluene	110	94
3	1,4-Dioxane	105	11
4	Heptane	100	0
5	1-Propanol	100	42
6	Ethyl Acetate	100	57
7[a]	Ethyl Acetate/H_2O	100	52
8	Acetonitirle	90	0
9[a]	Ethanol/H_2O	90	49
10	Ethanol	90	53
11	Petrol Ether (60-80)	90	21
12[a]	Petrol Ether (60-80)/H_2O	90	18
13	Hexane	90	55
14	Methanol	65	0
15[a]	Methanol/H_2O	65	0
16	H_2O	100	0

[a] Conversions are based on oxime and are determined by ^{1}H NMR analysis.

Conditions: Boronic aldoxime (0.2471 g, 1mmol), $Cu(OAc)_2$ (0.0045 g, 2.5 mol%), solvent (2 mL), 20 h; [a]9:1 Organic solvent:H_2O mixture.

Table 4.5. *Solvent and temperature screen.*

The solvent screen showed xylene and toluene at reflux gave the best conversion into primary amide **4.19** (Table 4.5, entries 1 and 2). Adding water to the reaction still gave conversion, so water does not cause any inhibitory effect on the copper acetate (Table 4.5, entries 7, 9, 12 and 15). Afterwards, we attempted to decrease the reaction temperature and reaction time (Tables 4.6 and 4.7).



4.10 4.19

Entry	Temperature (°C)	Conversion into 4.19(%)[a]
1	110	94
2	100	94
3	90	92
4	80	91
5	70	83
6	60	62

[a] Conversions are based on oxime and are determined by ^{1}H NMR analysis.

Table 4.6. *Temperature screen.*

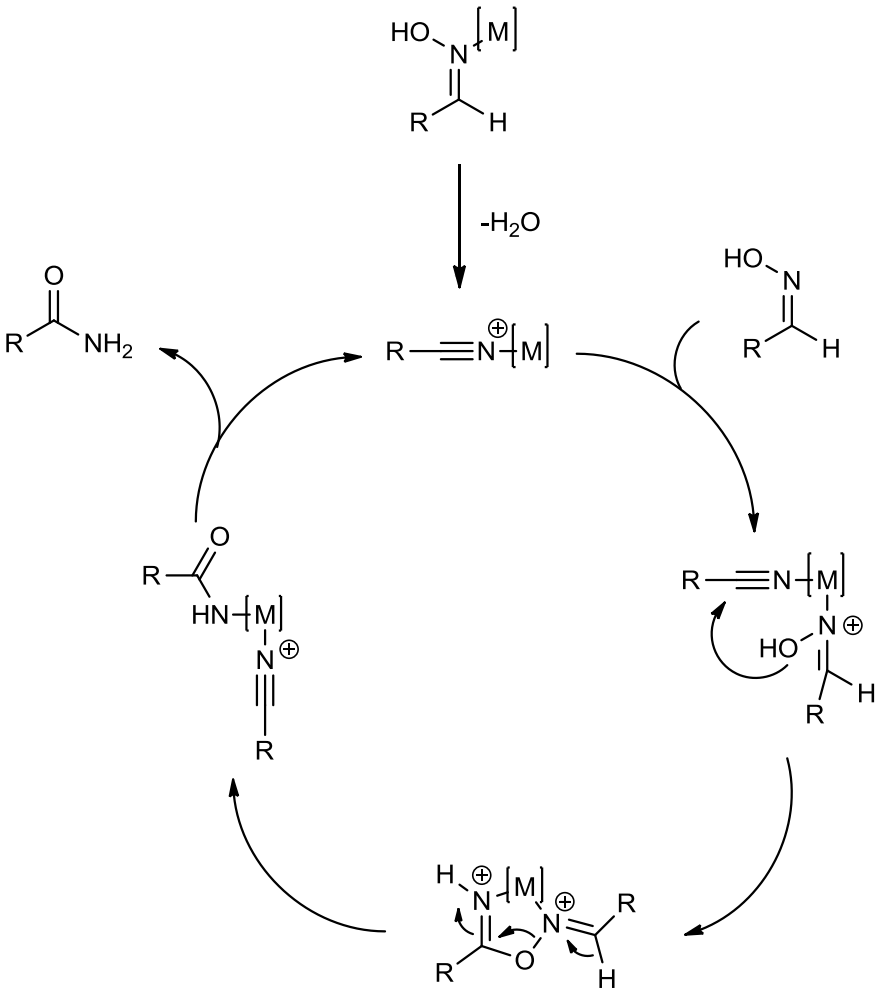
Entry	Time (h)	Conversion into 4.19(%)[a]
1	4	42
2	8	60
3	12	68
4	16	88
5	18	95
6	20	94
7	24	94

[a] Conversions are based on oxime and are determined by ^{1}H NMR analysis.

Table 4.7. *Time screen.*

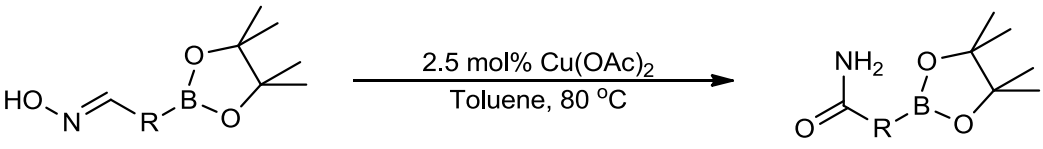
From these results, it was determined that a catalyst loading of 2.5 mol% copper

acetate was found to be optimal for the boronic amide formation by using toluene as solvent at 80 ^{o}C for 18 hours. The mechanism of aldoxime rearrangement into primary amide has been proposed by the Williams group. They used ^{18}O labelled oxime which suggested that a bimolecular mechanism was operating. Metal catalysts have been suggested to be a key intermediate in the mechanism which causes nucleophilic attack in the presence of an amine much easier.[113]



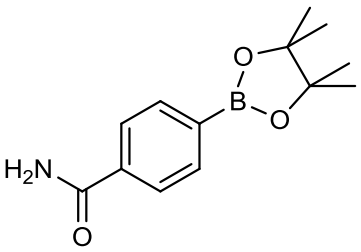
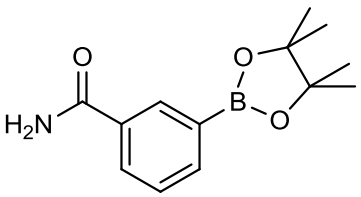
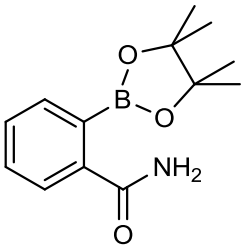
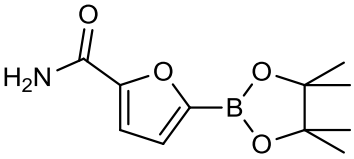
Scheme 4.10. *Proposed mechanism of aldoxime rearrangement into primary amide.*

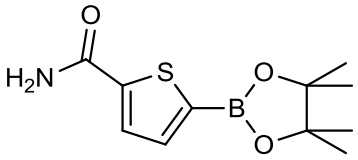
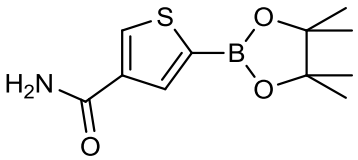
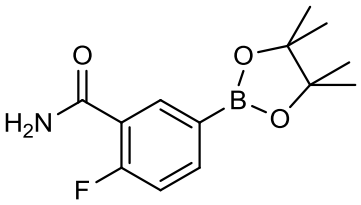
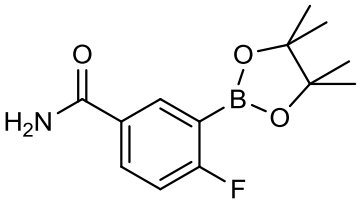
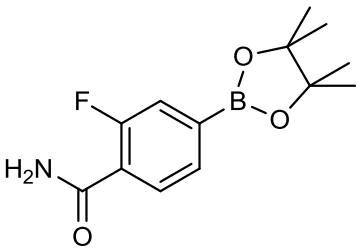
In order to show the general applicability of this method for the boronic amide formation, several boronic aldoximes were converted into the corresponding primary amides, although some were found to require longer reaction times and these findings have been reported recently.[114]



(R = phenyl, furan or thiophene)

Scheme 4.11. *Conversion of boronic oximes into amides.*

Entry		Boronic amide	Time (h)	Conversion into amide (%)[a]
1	**4.19**		18	95
2	**4.20**		18	91
3	**4.21**		18	0
4	**4.22**		18	84

5	**4.23**		18	88
6	**4.24**		18	84
7	**4.25**		24	78
8	**4.26**		24	75
9	**4.27**		24	80

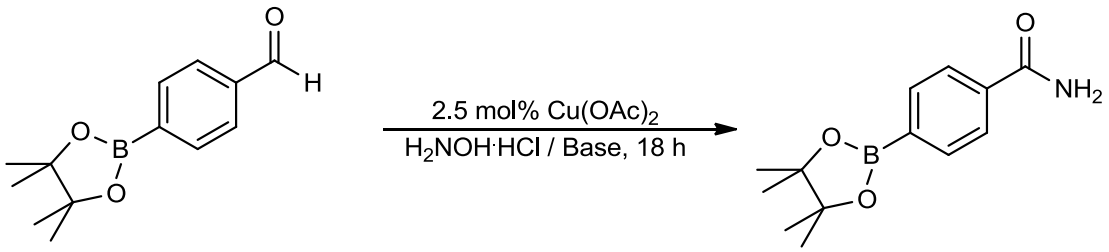
[a] Conversions are based on oxime and are determined by ^{1}H NMR analysis.

Conditions: Boronic aldoxime (2mmol), $Cu(OAc)_2$ (0.0091g, 2.5 mol%), PhMe (2mL), 80^{o}C.

Table 4.8. *Oximes screen with copper catalysts.*

Pleasingly, all reactions were successful under these conditions. Reactions were successful for the boronic phenyl amide formation (Table 4.8, entries 1-2, 7-9), the boronic furan amide formation (Table 4.8, entry 4) and the boronic thiophene amide formation (Table 4.8, entries 5 and 6). Specifically, steric hinderance around the reaction site (Table 4.8, entry 3) led to no conversion into boronic amide being observed.

A natural expansion of this reaction would be to start from boronic aldehyde and make the oxime *in situ* with hydroxylamine. We attempted to form boronic amide **4.19** by using boronic aldehyde **2.6** react with the hydroxylamine hydrochloride salt and an additional base in different solvents. Because hydroxylamine hydrochloride salt and base cannot dissolve in most organic solvents, we needed to blend organic solvent with water in some reactions (Table 4.9).



2.6 4.19

Scheme 4.12. *Synthesis of boronic aldehyde into amide.*

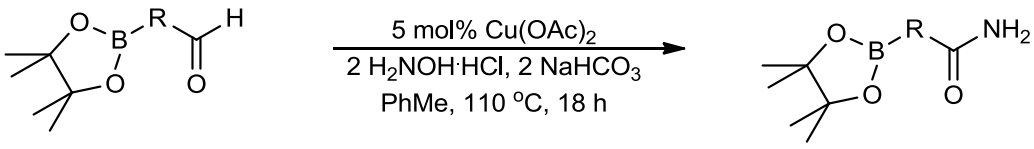
Entry	Solvent / Temperature (^{o}C)	Reaction conditions	Conversion into amide 4.19 (%)[a]
1	Xylene / 155^{o}C	a	0
2	Xylene / 155^{o}C	b	43
3	Xylene / 155^{o}C	c	58
4	Xylene / 155^{o}C	d	32
5	Toluene / 110^{o}C	a	0
6	Toluene / 110^{o}C	b	42
7	Toluene / 110^{o}C	c	65
8	Toluene / 110^{o}C	d	38
9[a]	Toluene & Water / 100^{o}C	a	0
10[a]	Toluene & Water / 100^{o}C	b	40
11[a]	Toluene & Water / 100^{o}C	c	58
12[a]	Toluene & Water / 100^{o}C	d	31

13	Ethyl Acetate / 100°C	a	0
14	Ethyl Acetate / 100°C	b	38
15	Ethyl Acetate / 100°C	c	50
16	Ethyl Acetate / 100°C	d	21
17[a]	Ethyl Acetate & Water / 100°C	a	0
18[a]	Ethyl Acetate & Water / 100°C	b	14
19[a]	Ethyl Acetate & Water / 100°C	c	36
20[a]	Ethyl Acetate & Water / 100°C	d	10
21	Ethanol / 100°C	a	0
22	Ethanol / 100°C	b	33
23	Ethanol / 100°C	c	46
24	Ethanol / 100°C	d	24
25[a]	Ethanol & Water / 100°C	a	0
26[a]	Ethanol & Water / 100°C	b	16
27[a]	Ethanol & Water / 100°C	c	37
28[a]	Ethanol & Water / 100°C	d	11
29[ab]	Toluene & Water / 100°C	e	89

[a] Conversions are based on aldehyde and are determined by ^{1}H NMR analysis.

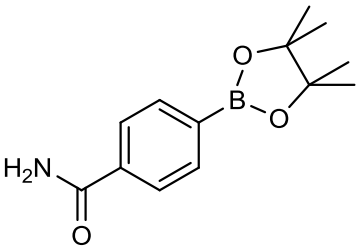
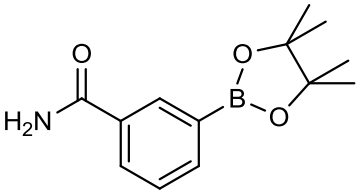
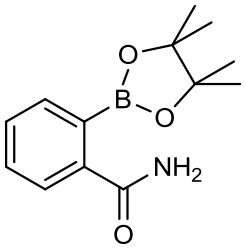
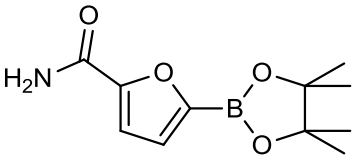
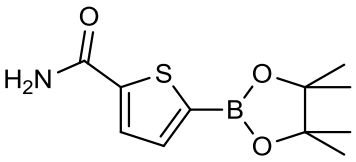
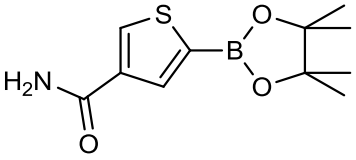
Conditions: (a) 1 equiv. $H_2NOH{\cdot}HCl$, no base; (b) 1 equiv. $H_2NOH{\cdot}HCl$, 1 equiv. Na_2CO_3; (c) 1 equiv. $H_2NOH{\cdot}HCl$, 1 equiv. $NaHCO_3$; (d) 1 equiv. $H_2NOH{\cdot}HCl$, 1 equiv. NaOAc; (e) 2 equiv. $H_2NOH{\cdot}HCl$, 2 equiv. Na_2HCO_3; [a]9:1 Organic solvent:H_2O mixture; [b]5 mol% $Cu(OAc)_2$; atmosphere of nitrogen.

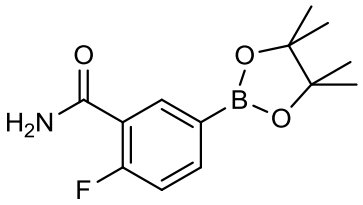
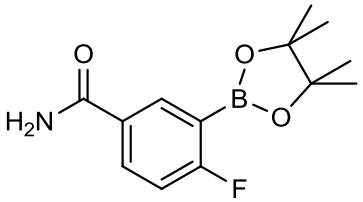
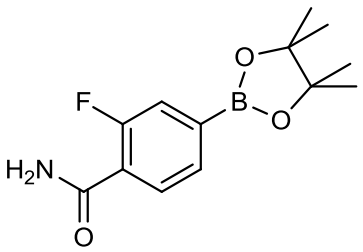
Table 4.9. *Aldehyde to amide reaction conditions screen.*



(R = phenyl, furan or thiophene)

Scheme 4.13. *Synthesis of boronic aldehyde into amide.*

Entry		Boronic amide	Time (h)	Conversion into amide (%)[a]	Isolated yield (%)
1	**4.19**		18	91	83
2	**4.20**		18	87	79
3	**4.21**		18	0	0
4	**4.22**		18	82	75
5	**4.23**		18	76	70
6	**4.24**		18	64	57

7	**4.25**		24	74	65
8	**4.26**		24	71	66
9	**4.27**		24	78	72

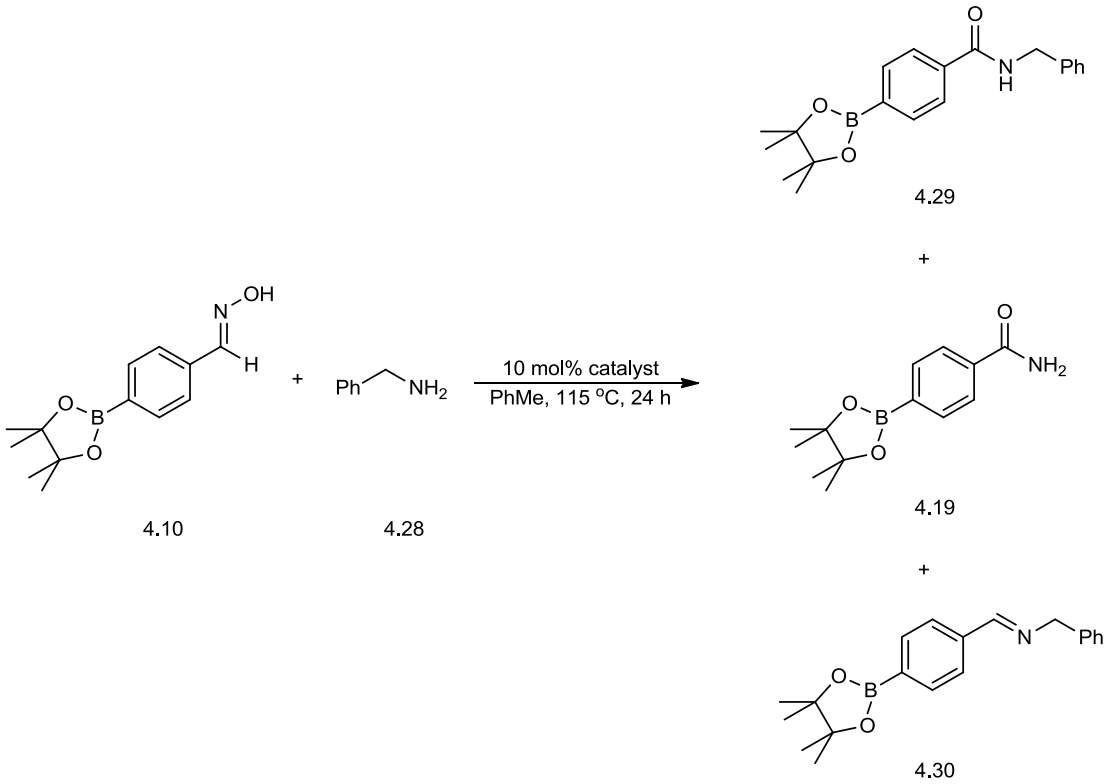
[a] Conversions are based on aldehyde and are determined by ^{1}H NMR analysis.

Table 4.10. *Aldehydes screen with copper catalysts.*

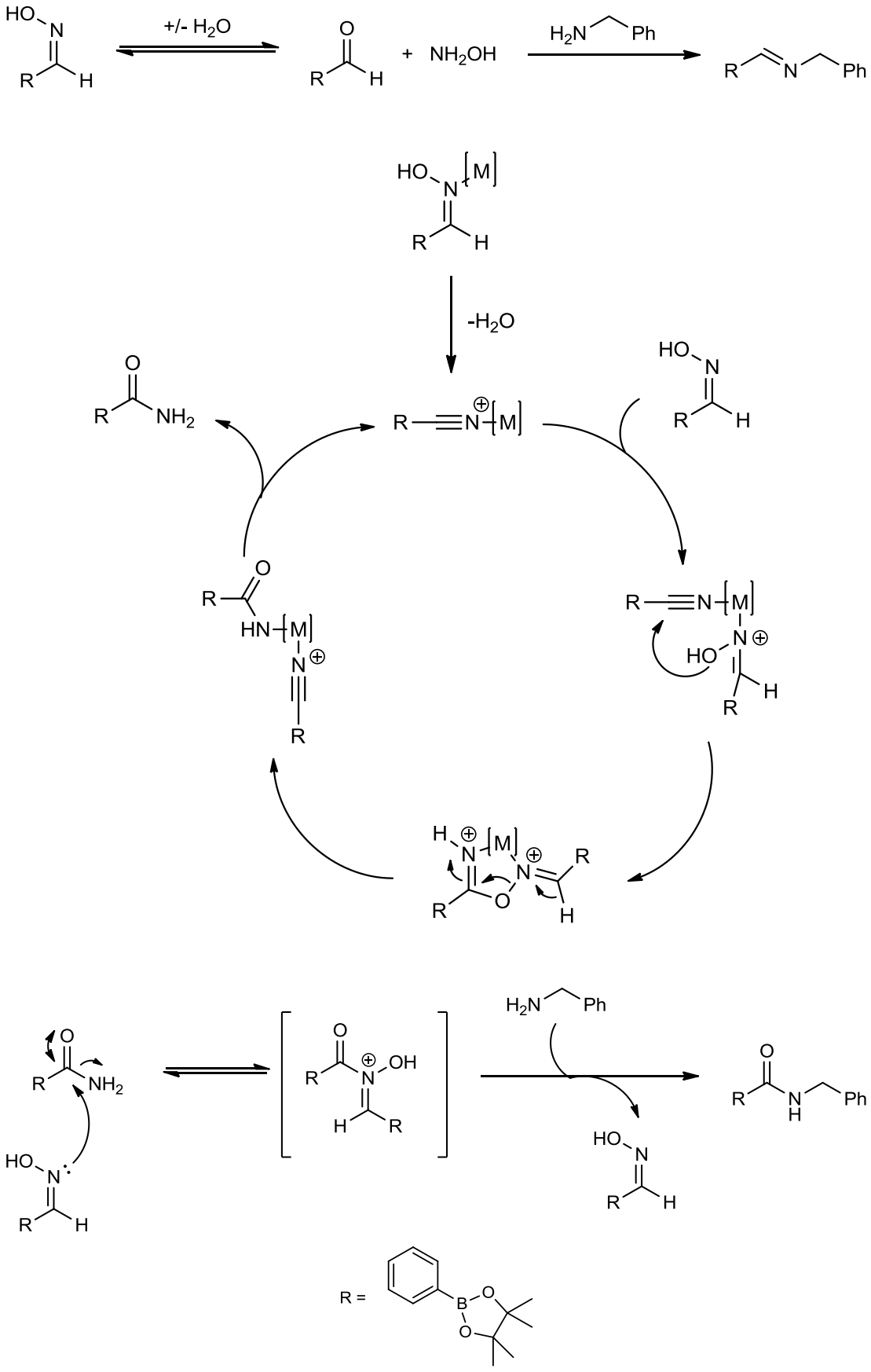
On the basis of these results, using 5 mol% copper acetate, 2 equiv. of hydroxylamine hydrochloride and 2 equiv. of sodium hydrogen carbonate were found to be suitable conditions for primary boronic amide formation. Several boronic aldehydes were converted into the corresponding primary amides in good or excellent yields. The conversions of all of them were very close. However, groups in the ortho position again hindered the reaction (Table 4.10, entry 3) and the conversion into the primary boronic amide dropping for one substrate (Table 4.10, entry 6) as well which could possibly be due to the same reason.

4.5 Secondary amide formation

After we found the method for the rearrangement of a boronic aldoxime into a primary amide, we decided to focus on identifying a suitable catalyst for the conversion of a boronic aldoxime into a secondary amide. We chose the reaction of boronic aldoxime **4.10** with benzylamine **4.28** as a model reaction (Scheme 4.14). The reaction gave three different products and the proposed mechanisms were presented in scheme 4.15.



Scheme 4.14. *Reaction of boronic aldoxime with benzylamine into secondary amide.*



Scheme 4.15. *Proposed mechanism of aldoxime rearrangement into imine, primary amide and secondary amide.*

The mechanism of aldoxime rearrangement into primary amide has been investigated by the Williams group. They used ^{18}O labelled oxime suggested that a bimolecular mechanism was operating. Metal catalysts have been suggested to be a key intermediate in the mechanism which causes nucleophilic attack in the presence of an amine to be much easier.[113]

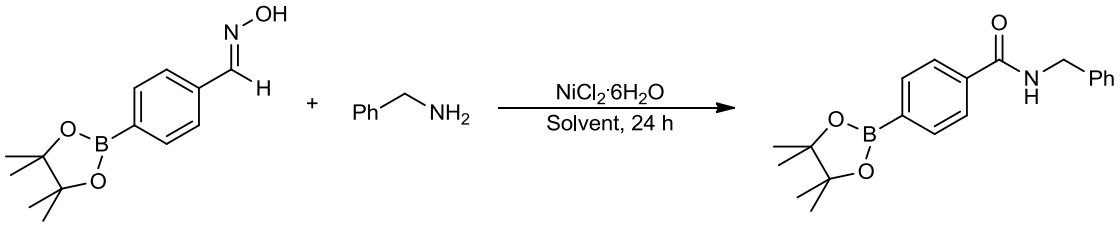
The catalysts screened were those known to catalyse the rearrangement of a boronic aldoxime into primary amine (Table 4.11).

Entry	Catalyst	Conversion into 126 (%)[a]	Conversion into 123 (%)[a]	Conversion into 127 (%)[a]
1	$Cu(OAc)_2$	35	0	65
2	$CuCl_2$	0	33	14
3	$Pd(OAc)_2$	0	73	27
4	$PdCl_2$	0	11	0
5	$NiCl{\cdot}6H_2O$	55	0	45
6	$NiBr_2$	43	0	57

[a] Conversions are based on oxime and are determined by ^1H NMR analysis.

Table 4.11. *Initial catalyst screen of secondary amide formation.*

From all of the results above, none of catalysts were good for this reaction. The use of copper acetate (Table 4.11, entry 1) led mainly to the formation of imine **4.30**. Palladium acetate (Table 4.11, entry 3) was more successful giving the primary amide **4.19** as the major product. We only found that $NiCl_2$ gave an acceptable conversion into the secondary amide and we did further reactions to try to improve the selectivity (Scheme 4.16, Table 4.12).



4.10 4.28 4.29

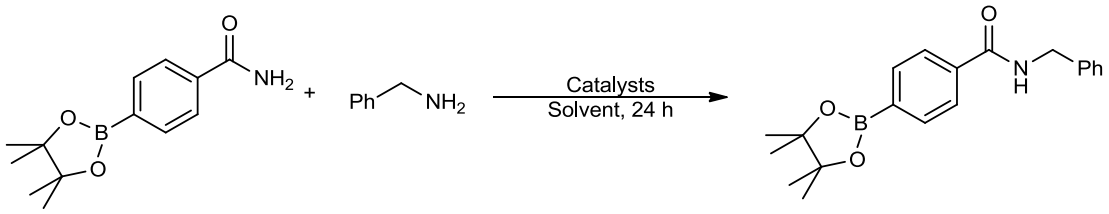
Scheme 4.16. *Reaction of boronic aldoxime with benzylamine into secondary amide.*

Entry	Mol % catalyst	Solvent	Temperature (°C)	Conversion into 4.29 (%)[a]
1	50	PhMe	115	60
2	30	PhMe	115	58
3	20	PhMe	115	55
4	50	*p*-xylene	155	68
5	30	*p*-xylene	155	61
6	20	*p*-xylene	155	55

[a] Conversions are based on oxime and are determined by ^{1}H NMR analysis.

Table 4.9. *Temperature and catalysts amount screen.*

The results in table 4.9 show that the highest conversion was 68% at the temperature 155 ^{o}C and a catalyst loading of 50 mol% was required. We didn't try any other catalysts or other conditions to improve the conversion. We decided to do the next step which was to find a suitable catalyst for the conversion of a primary amide into a secondary amide. We selected the reaction of primary boronic amide **4.19** with benzylamine **4.28** as a model reaction (Scheme 4.17).



4.19 4.28 4.29

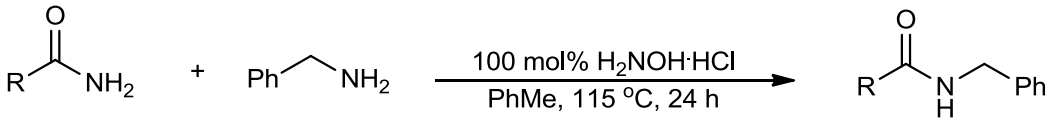
Scheme 4.17. *Reaction of primary boronic amide and benzylamine.*

Entry	Catalysts	Mol % catalyst	Solvent	Temperature (°C)	Conversion into 4.29 (%)[a]
1	$Cu(OAc)_2$	10	PhMe	115	77
2	$Pd(OAc)_2$	10	PhMe	115	56
3	$NiCl_2 \cdot 6H_2O$	10	PhMe	115	71
4	$H_2NOH \cdot HCl$	100	PhMe	115	98
5	$Cu(OAc)_2$	10	*p*-xylene	155	77
6	$Pd(OAc)_2$	10	*p*-xylene	155	54
7	$NiCl_2 \cdot 6H_2O$	10	*p*-xylene	155	72
8	$H_2NOH \cdot HCl$	100	*p*-xylene	155	99

[a] Conversions are based on primary amide and are determined by ^{1}H NMR analysis.

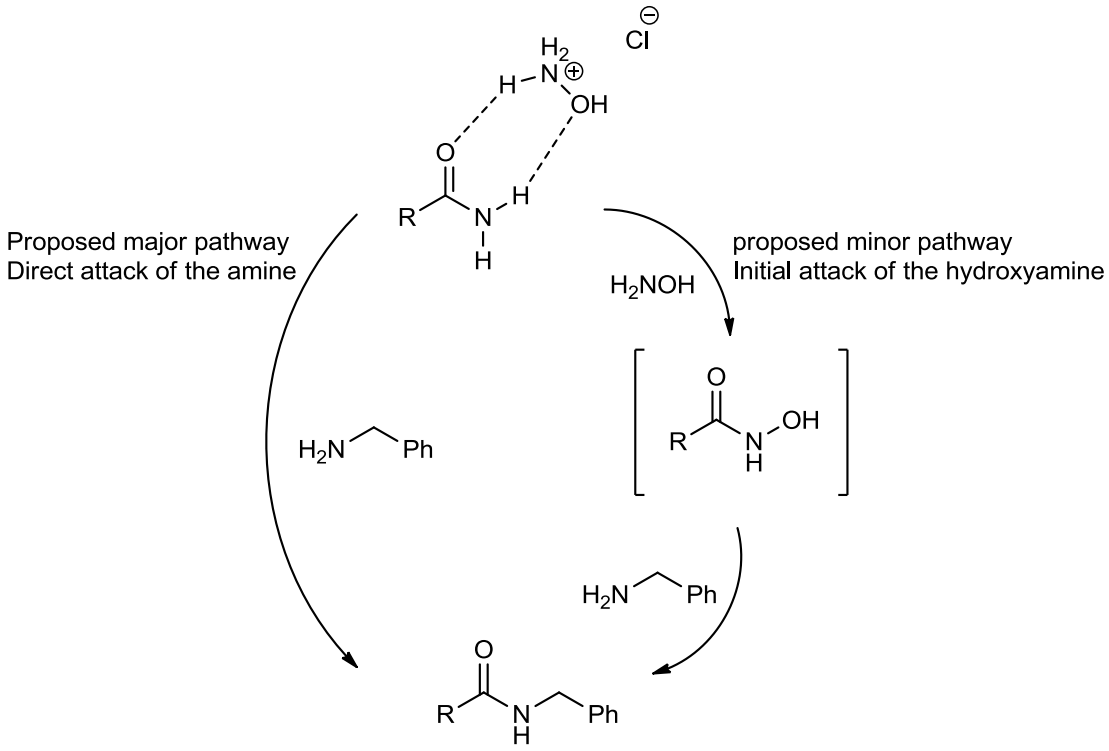
Table 4.10. *Solvents and catalysts amount screen.*

From the results in Table 4.10 it is clear that hydroxylamine hydrochloride alone gives the best conversion for this reaction. Although we need to use stoichiometric amounts, the reduction in cost far outweighs not requiring the use of a transition metal catalyst.



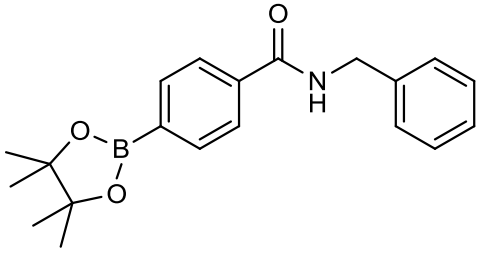
4.28

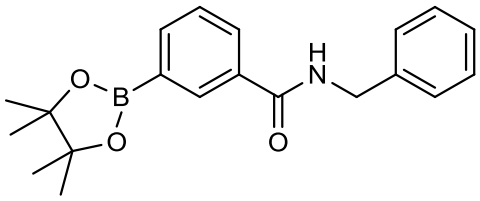
Scheme 4.18. *Reaction of primary boronic amide and benzylamine.*



Scheme 4.19. *Proposed reaction pathways.*

The major pathway in this reaction is attack of the amine onto the hydrogen bonded primary amide-hydroxylamine complex. This proposed mechanism of primary amide activation *via* a hydrogen bonding complex is presented by the Williams group with ^{1}H NMR studies.[114]

Entry		Boronic amide	Conversion into amide (%)[a]	Isolated yield (%)
1	**4.29**		100	94

2	**4.31**		100	90

[a] Conversions are based on primary amide and are determined by ^{1}H NMR analysis.

Table 4.11. *Formation of secondary amide.*

In summary, the rearrangement of boronic aldoximes into primary amides has been shown to be catalysed by cheap and simple metal catalyst copper acetate. The formation of secondary amides was found to proceed *via* the primary amide and a subsequent reaction with the amine present. This reaction is catalysed by the hydroxylamine hydrochloride. Although we tried to do the rearrangement of boronic aldoxime into secondary amide using cooper acetate or other catalysts, the major product we obtained was the imine. In future work, it intends to use the known conditions to synthesise different secondary boronic amide. Secondly, it is going to find out the suitable catalyst and conditions for the rearrangement of boronic aldoximes into secondary amides and tertiary amides.

5 Conclusion of results and discussion

In conclusion, my research is presented in two main sections: the first involves employing a protected boronic acid alcohol or a protected boronic amine as agents for the formation of new boronic acid compounds. It was discovered that the $[Ru(p\text{-cymene})Cl_2]_2$/DPEphos/$Na_2CO_3$ combination was best suited for this transformation *via* borrowing hydrogen and optimisation of the reaction was also carried out. This conditions were found to be successful for one pot reaction (Suzuki reaction and Borrowing Hydrogen reaction) as well. In the further research, we found that we can use the borrowing hydrogen method to synthesize more fluorescent sensors in a much easier fashion.

The second part is the successful development of a copper-catalysed to synthesise amide bonds. By using 5 mol% copper acetate, 2 equiv. of hydroxylamine hydrochloride and 2 equiv. of sodium hydrogen carbonate were found to be suitable for primary boronic amide and the conversion into primary amide when staring from the aldehyde or the oxime. The formation of secondary amides was found to proceed *via* the primary amide and a subsequent reaction with the amine present. This reaction is catalysed by hydroxylamine hydrochloride. The research for forming more secondary boronic amides is still ongoing.

6 Experimental

6.1 Genaral Experimental Methods

All reactions requiring an anhydrous, inert atmosphere were carried out under an argon or nitrogen atmosphere using Dean-Stark, Schlenk line techniques or use of Radley's or Young's tap carousel tubes. All reaction reagents were purchased from commercial suppliers: Sigma-Aldrich, Fisher, Lancaster, Frontier Scientific and TCI. All solvents were distilled or obtained and stored in the presence of 3 Å molecular sieves prior to use.

TLC was carried out on aluminium or glass backed plates covered with neutral silica was used to monitor reactions where appropriate. These plates were visualised by 254nm UV light, followed by further visualisation using vanillin, $KMnO_4$ or ninhydrin as required. Organic layers were usually dried with $MgSO_4$ and concentrated *in vacuo*. If necessary, high vacuum was used for further drying. For further purification, flash column chromatography was carried out using 60 Å silica gel purchased from Fisher Scientific.

^1H NMR and ^{13}C NMR spectra were run in $CDCl_3$ or d_4-MeOD using a Bruker Avance 250 (250 MHz) or Bruker Avance 300 (300 MHz). Chemical shifts are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) unless otherwise stated. In ^1H NMR coupling constants (***J***) are recorded in Hz and signal multiplicities are reported as singlet (s), doublet (d), triplet (t). quartet (q), doublet to doublet (dd), doublet of triplets (dt), triplet of triplets (tt), pentet (p), unresolved multiplet (m), broad (br.) or apparent (app.).

For mass spectrometry data, a micrOTOF electrospray time-of-flight (ESI-TOF) mass

spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). 10 µL of sample was injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10 µL of a calibrant of 5mM sodium formate was injected after the sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

6.2 Fluorescence measurements

Buffer solution

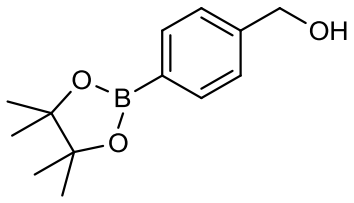
The fluorescence titrations of boronic acid sensors with different saccharides were carried out in a pH 8.21 aqueous methanolic buffer. The buffer was prepare by 52.1 wt% HPLC grade methanol in deionised water with 2.752 mmol/L of KH_2PO_4, 2.757 mmol/L Na_2HPO_4 and 0.01 mol/L of KCl. The buffer solution need to be stored at 4 ^{o}C in the dark when is not used.

Fluorescence saccharide titration

In each instance the required sensor was weighed out in a 100 mL volumetric flask and then was made up to the required volume with HPLC grade methanol to generate a stock solution of know molarities. The stock solution was transferred *via* micro-syringe to a flask which was containing the pH 8.21 aqueous methanolic buffer (the buffer solution was strring). Fluorescence spectra were recorded as increasing concentration of saccharides. Saccharides were added to the stirred sensor solution and recored in an intercal of 5 mins. The typical fluorescence response was evaluated over a saccharide concentration range from 0 to 0.3 mol/L.

6.3 Experimental Procedures for Chapter 2

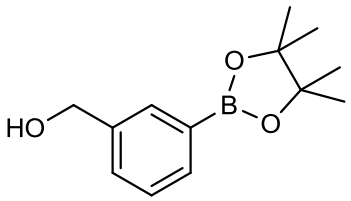
6.3.1 General Procedure I for the Preparation of (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



2.6

(4-(Hydroxymethyl)phenyl)boronic acid (3.81 g, 25 mmol) and pinacol (3.54 g, 30 mmol) were mixed in toluene (300 mL) in a round-bottomed flask. A Dean Stark head was fitted and the reaction was heated under reflux for 2 hours. The mixture was allowed to cool to room temperature, and then washed with water (3 x 150 mL). The organic layer was condensed under reduced pressure and DCM (100mL) was added. This was washed with water (3 x 150 mL), dried over $MgSO_4$ and filtered. The solvents were again removed under reduced pressure to yield compound **2.6** as a colourless solid (4.84 g, 82.7%); m.p.: 74-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.84 (2H, d, *J* = 7.8 Hz, Ar**H**), 7.40 (2H, d, *J* = 7.8 Hz, Ar**H**), 4.75 (2H, s, PhC**H**$_2$OH), 1.38 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 144.1, 135.1, 126.1, 83.8, 65.2, 24.8; ESI-MA: Calculated for $C_{13}H_{19}BNaO_3$ $[M+Na]^+$:257.1319. Found: 257.1336.

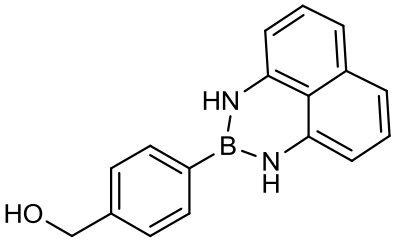
6.3.2 General Procedure II for the Preparation of (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



2.7

(3-(Hydroxymethyl)phenyl)boronic acid (3.04 g, 20 mmol) and pinacol (2.83 g, 24 mmol) were mixed in toluene (150 mL). A Dean-Stark head was fitted and the reaction was heated under reflux for 2 hours. The mixture was allowed to cool to room temperature, and then washed with water (3 x 100 mL). The organic layer was condensed under reduced pressure and DCM (100 mL) was added. This was washed with water (3 x 100 mL), dried over $MgSO_4$ and filtered. The solvents were again removed under reduced pressure to yield **2.7** as a colourless solid (4.15 g, 88.7%); m.p.: 42-46°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.83 (1H, s, Ar**H**), 7.77 (1H, d, *J* = 6.9 Hz, Ar**H**), 7.52 (1H, d, *J* = 6.9 Hz, Ar**H**), 7.41 (1H, t, *J* = 6.9 Hz, Ar**H**), 4.73 (2H, s, PhC**H**$_2$OH), 1.38 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 140.1, 134.1, 133.3, 130.1, 128.1, 83.9, 65.3, 24.9; ESI-MA: Calculated for $C_{13}H_{19}BNaO_3$ $[M+Na]^+$: 257.1319. Found: 257.1321.

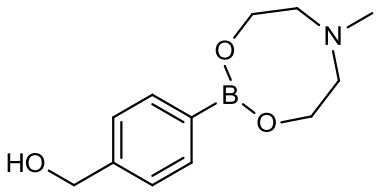
6.3.3 General Procedure III for the Preparation of boronamide



2.13

To a 100 mL round-bottomed flask was added 4-(hydroxymethyl)-phenylboronic acid (1.52 g, 10 mmol), 1,8-diaminonaphthalene (1.58 g, 5 mmol), toluene (40 mL) and DMSO (3.5 mL). The flask was fitted with a Dean stark tap filled with toluene. The Dean-Stark trap was fitted with a water-cooled reflux condenser vented to ambient atmosphere. The stirred solution was refluxed with azeotropic removal of water for 12 h. The solution was then transferred to a 125 mL separatory funnel, diluted with EtOAc (40 mL), and washed with water (40 mL) and organic layer was dried over $MgSO_4$ and concentrated in vacuum. These compounds were dissolved in the minimal amount of acetone and celite added to the flask and shaken. This mixture was then filtered through a plug of celite and washed with acetone until the solution is colourless. The solution was concentrated *in vacuo* and the resulting powder was subjected to flash chromatography on silica gel (hexanes:EtOAc 50:50) to afford **2.13** as a pale purple solid (1.03 g, 75.3%); m.p.: 170-172 °C; ^{1}H NMR (300 MHz, MeOD, 25 °C): δ 7.71 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.30 (2H, d, *J* = 7.7 Hz, nap.), 7.00-6.91 (2H, m, nap.), 6.81 (2H, dd, *J* = 8.2, 0.8 Hz, Ar**H**), 6.41 (2H, dd, *J* = 7.7, 0.9 Hz, nap.), 4.54 (2H, s, PhC**H**$_2$OH); ^{13}C NMR (75.5 MHz, MeOD, 25 °C): δ 144.7, 144.1, 138.3, 133.7, 128.9, 127.8, 121.7, 118.2, 107.1, 65.6; ESI-MA: Calculated for $C_{17}H_{15}BN_2NaO$ $[M+Na]^+$: 297.1175. Found: 297.1158.

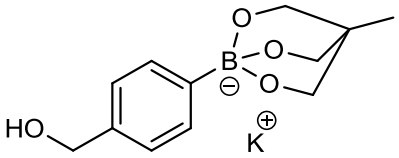
6.3.4 General Procedure IV for the Preparation of MIDA boronate



2.16

To a 100 mL round-bottomed flask was added 4-(hydroxymethyl)phenylboronic acid (1.52 g, 10 mmol), *N*-methyldiethanolamine (1.145 mL, 10 mmol) and acetone (50 mL). The flask was fitted with a short-path distillation apparatus. The mixture was distilled with periodic addition of acetone to maintain a volume of 20 to 40 mL. When 95 mL of distillate was collected, the distillation was stopped. The suspension from the distillation pot was transferred to a 500 mL round-bottomed flask and then diluted with acetone to a volume of 400 mL. The mixture was filtered through a pad of celite, and the solution was concentrated *in vacuo* to a minimum volume. The solution was then diluted with Et_2O (500 mL), gently agitated, and left to stand at 0 ºC for 2 h. The resulting crystalline solid was collected via vacuum filtration to afford the pure product as a colorless, crystalline solid **2.16** (1.64 g, 69.7%); m.p.: 196-198 °C; ^{1}H NMR (250 MHz, MeOD, 25 °C): δ 7.55 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.28 (2H, d, *J* = 7.9 Hz, Ar**H**), 4.57 (2H, s, PhC**H**$_2$OH), 4.18 - 4.03 (4H, m, O(C**H**$_2$CH$_2$)$_2$N), 3.30 (4H, dd, *J* = 3.3, 1.6 Hz, O(CH$_2$C**H**$_2$)$_2$N), 2.31 (3H, s, NCH$_3$); ^{13}C NMR (75.5 MHz, MeOD, 25 °C): δ 142.3, 134.7, 127.6, 127.4, 65.8, 63.5, 61.5, 60.8; ESI-MA: Calculated for $C_{12}H_{19}BNO_3$ $[M+H]^+$: 236.1458. Found: 236.1435.

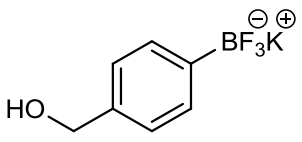
6.3.5 General Procedure V for the Preparation of potassium triolborate



2.20

4-(Hydroxymethyl)phenylboronic acid (1.52 g, 10 mmol) and 1,1,1-tris (hydroxymethyl) ethane (1.32 g, 11 mmol) were dissolved in toluene (100 mL). Water was removed by azeotropic distillation by the Dean stark method for 4 hours. The solution was concentrated *in vacuo* to give crude compound. The crude mixture and KOH (0.56 g, 10 mmol) were dissolved in toluene and heated at reflux for 4 hours by the Dean Stark method. The compound **2.20** that precipitated was collected by filtration, washed with acetone, and all solvent removed under vacuum to give the title compound as a colourless solid (2.16 g, 79%), m.p.: 187-189 °C, ^{1}H NMR (250 MHz, MeOD, 25 °C): δ 7.71 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.29 (2H, d, *J* = 8.1 Hz, Ar**H**), 4.59 (2H, s, PhC**H**$_2$OH), 3.76 (6H, bro, 3 x OC**H**$_2$CCH$_3$), 0.95 (3H, s, OCH$_2$CC**H**$_3$); ^{13}C NMR (75.5 MHz, MeOD, 25 °C): δ 145.5, 135.4, 127.3, 116.4, 66.8, 65.6, 38.3, 18.1; ESI-MA: Calculated for $C_{12}H_{17}BO_4$ $[M+H]^+$: 236.1220. Found: 236.1231

6.3.6 General Procedure VI for the Preparation of potassium trifluoroborate

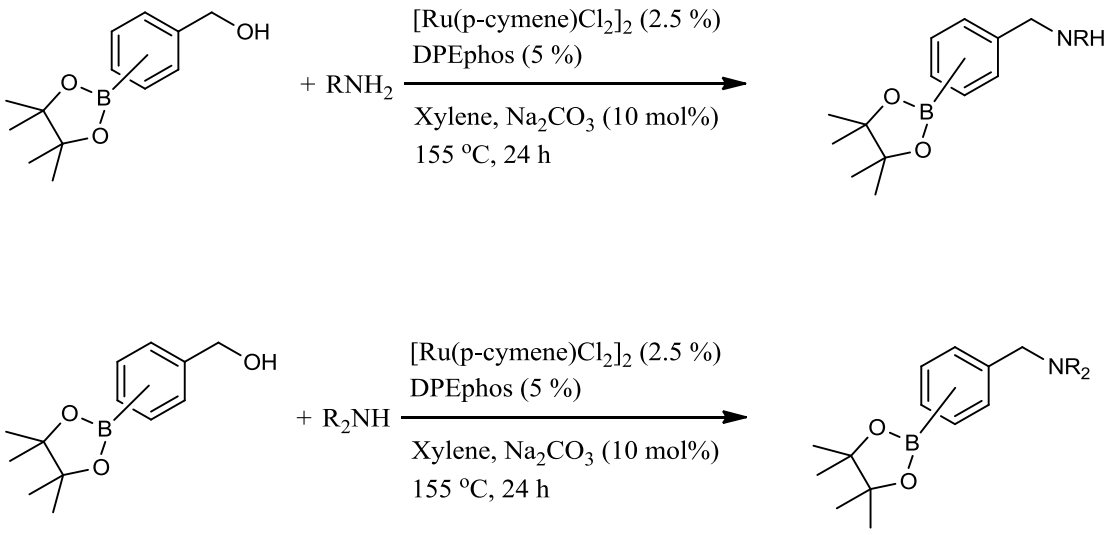


2.22

Boronic ester alcohol (1.17 g, 5 mmol) was stirred at room temperature in a 1:1

mixture of methanol and water (0.1 M) in plastic apparatus. KHF_2 (1.14 g, 30 mmol) was added in one portion and all reagents were stirred at room temperature overnight. The solution were evaporated to dryness and redissolved in hot acetone and filtered. The filtrate was evaporated *in vacuo* and the compound was triturated with ether three times. The solid was further redissolved in acetone, and then dried *in vacuuo* to give the product **2.22** as a colourless solid (0.67 g, 63%), m.p.: 209-211 °C, ^{1}H NMR (250 MHz, MeOD, 25 °C): δ 7.66 (2H, d, *J* = 6.0 Hz, Ar**H**), 7.33 (2H, dd, *J* = 6.0, 1.9 Hz, Ar**H**), 5.12 (2H, s, PhC**H**$_2$OH); ^{13}C NMR (75.5 MHz, MeOD, 25 °C): δ 130.5, 127.8, 126.9, 121.6, 70.7; ESI-MA: Calculated for $C_7H_8BF_3O$ $[M+H]^+$: 176.0620. Found: 176.0644.

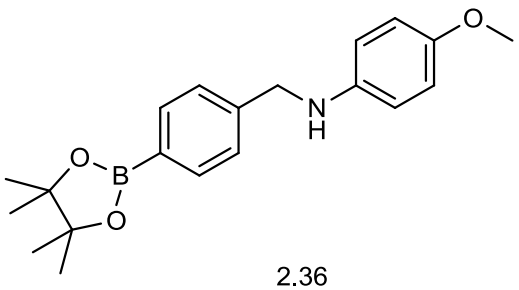
6.3.7 General Procedure VII for the Ruthenium-catalysed N-Alkylation of amine with boronic ester alcohol by borrowing hydrogen



To an oven-dried, nitrogen-purged Radley's carousel tube containing [Ru(*p*-cymene)Cl_2]$_2$ (15.3 mg, 0.025 mmol), DPEphos (53.8 mg, 0.05 mmol), Na_2CO_3 (10.6 mg, 0.1 mmol), xylene (2 mL), amine (1 mmol) and boronic ester alcohol (1 mmol). The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature and then the temperature increased to 155 °C for 24 hours. The

resulting crude compounds were evaporated *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of boronic ester alcohol and amine products in the proton NMR spectrum of the crude reaction mixture. All products were purified by recrystallised using DCM:Hexane (1:20).

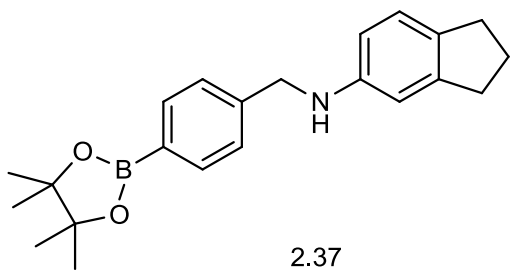
N-(4-methoxybenzyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (Entry 1, Table 2.17)



2.36

Following **general procedure VII**, used boronic ester alcohol (0.2345 g, 1 mmol) and p-Anisidine (0.1243 g, 1 mmol) to give the title compound as a purple oil (0.25 g, 72%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.71 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.30 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.69 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.52 (2H, d, *J* = 9.0 Hz, Ar**H**), 4.23 (2H, s, PhC**H**$_2$NH), 3.66 (3H, s, OC**H**$_3$), 1.27 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 152.2, 142.9, 142.2, 135.1, 127.7, 126.8, 114.9, 114.2, 83.7, 55.8, 49.4, 24.9; ESI-MA: Calculated for $C_{20}H_{27}BNO_3$ $[M+H]^+$: 340.2084. Found: 340.2082.

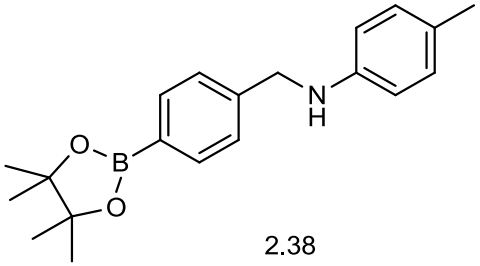
N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-2,3-dihydro-1H-inden-5-amine (Entry 2, Table 2.17)



2.37

Following **general procedure VII**, used boronic ester alcohol (0.2362 g, 1 mmol) and 5-Aminoindan (0.1332 g, 1 mmol) to give the title compound as a black oil (0.25 g, 72%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.82 (1H, s, Ar**H**), 7.73 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.29 (2H, d, *J* = 8.0 Hz, Ar**H**), 6.93 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.42 (1H, d, *J* = 8.1 Hz, Ar**H**), 4.64 (2H, s, PhC**H**$_2$NH), 2.73 (4H, dd, *J* = 13.8, 7.1 Hz, Ph(C**H**$_2$)$_2$CH$_2$), 1.98 (2H, dp, *J* = 22.0, 7.3 Hz, Ph(CH$_2$)$_2$C**H**$_2$), 1.27 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 145.5, 144.06, 135.6, 127.8, 126.1, 124.7, 113.3, 111.5, 83.8, 65.2, 31.9, 25.7, 24.8; ESI-MA: Calculated for $C_{22}H_{29}BNO_2$ $[M+H]^+$: 350.2291. Found: 350.2215.

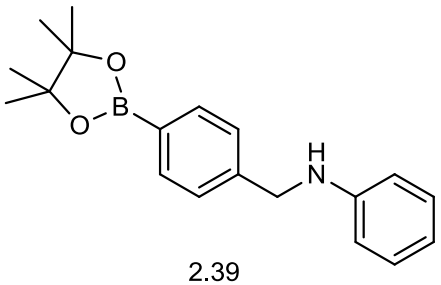
4-methyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)aniline (Entry 3, Table 2.17)



2.38

Following **general procedure VII**, used boronic ester alcohol (0.2348 g, 1 mmol) and p-Toluidine (0.1073 g, 1 mmol) to give the title compound as a brown oil (0.23 g, 70%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.79 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.38 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.97 (2H, d, *J* = 8.0 Hz, Ar**H**), 6.55 (2H, d, *J* = 8.0 Hz, Ar**H**), 4.32 (2H, s, PhC**H**$_2$NH), 2.23 (3H, s, PhC**H**$_3$), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 145.8, 142.9, 135.1, 129.8, 127.8, 126.7, 120.8, 113.1, 83.7, 48.7, 24.9, 21.6; ESI-MA: Calculated for $C_{20}H_{27}BNO_2$ $[M+H]^+$: 324.2135. Found: 324.2162.

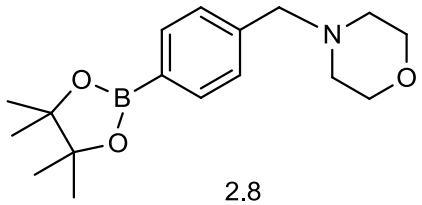
N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)aniline (Entry 4, Table 2.17)



2.39

Following **general procedure VII**, used boronic ester alcohol (0.2366 g, 1 mmol) and aniline (0.129 mL, 1 mmol) to give the title compound as a dark brown oil (0.16 g, 52%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.81 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.39 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.17 (3H, t, *J* = 7.8 Hz, Ar**H**), 6.63 (2H, d, *J* = 7.8 Hz, Ar**H**), 4.35 (2H, s, PhC**H**$_2$NH), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 148.1, 142.7, 135.1, 129.2, 126.7, 117.6, 112.9, 83.8, 48.4, 24.9; ESI-MA: Calculated for $C_{19}H_{25}BNO_2$ $[M+H]^+$: 310.1978. Found: 310.2001.

4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine (Entry 1, Table 2.19)

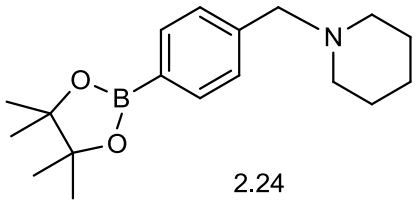


2.8

Following **general procedure VII**, used boronic ester alcohol (0.2347 g, 1 mmol) and Morpholine (0.09 mL, 1 mmol) to give the title compound as a yellow solid (0.25 g, 84 %), m.p.: 87-89 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.70 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.28 (2H, d, *J* = 8.0 Hz, Ar**H**), 3.64 (4H, t, N(CH$_2$C**H**$_2$)$_2$O), 3.45 (2H, s, PhC**H**$_2$N), 2.38-2.35 (4H, t, N(C**H**$_2$CH$_2$)$_2$O), 1.27 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz,

$CDCl_3$, 25 °C): δ 134.8, 128.6, 83.8, 66.9, 63.1, 53.6, 24.9; ESI-MA: Calculated for $C_{17}H_{27}BNO_3$ $[M+H]^+$: 304.2084. Found: 304.2083.

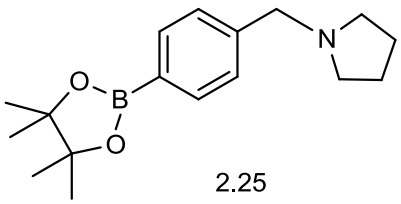
1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (Entry 2, Table 2.19)



2.24

Following **general procedure VII**, used boronic ester alcohol (0.2366 g, 1 mmol) and piperidine (0.098 mL, 1 mmol) to give the title compound as a dark red solid (0.24 g, 80%), m.p.: 97-99 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.69 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.26 (2H, d, *J* = 8.0 Hz, Ar**H**), 3.42 (2H, s, PhC**H**$_2$N), 2.34-2.23 (4H, m, N(C**H**$_2$CH$_2$)$_2$CH$_2$), 1.48 (4H, dd, *J* = 10.5, 5.5 Hz, N(CH$_2$C**H**$_2$)$_2$CH$_2$), 1.36-1.27 (2H, m, N(CH$_2$CH$_2$)$_2$C**H**$_2$), 1.26 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 134.6, 128.6, 83.7, 63.9, 54.5, 25.9, 24.8, 24.3; ESI-MA: Calculated for $C_{18}H_{29}BNO_2$ $[M+H]^+$: 302.2291. Found: 302.2376.

1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pyrrolidine (Entry 3, Table 2.19)

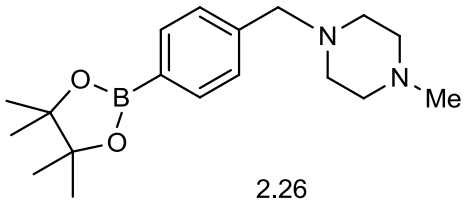


2.25

Following **general procedure VII**, used boronic ester alcohol (0.2345 g, 1 mmol) and Pyrrolidine (0.083 mL, 1 mmol) to give the title compound as a dark brown oil (0.22 g, 75%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.69 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.27 (2H, d, *J* =

8.0 Hz, Ar**H**), 3.56 (2H, s, PhC**H**$_2$N), 2.45-2.40 (4H, m, N(C**H**$_2$CH$_2$)$_2$), 1.73-1.68 (4H, m, N(CH$_2$C**H**$_2$)$_2$), 1.26 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 134.7 128.2, 83.7, 60.7, 54.1, 24.8, 23.4; ESI-MA: Calculated for $C_{17}H_{27}BNO_2$ $[M+H]^+$:288.2135. Found: 288.2185.

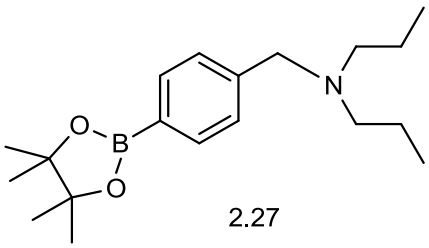
1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine (Entry 4, Table 2.19)



2.26

Following **general procedure VII**, used boronic ester alcohol (0.2365 g, 1 mmol) and 1-Methylpiperazine (0.11 mL, 1 mmol) to give the title compound as a dark brown oil (0.26 g, 83%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.69 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.26 (2H, d, *J* = 8.0 Hz, Ar**H**), 3.44 (2H, s, PhC**H**$_2$N), 2.38 (8H, bro, N(C**H**$_2$C**H**$_2$)$_2$N), 2.21 (3H, s, NC**H**$_3$), 1.26 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 141.6, 134.7, 128.5, 83.7, 63.1, 55.1, 53.1, 46.1, 21.9; ESI-MA: Calculated for $C_{18}H_{30}BN_2O_2$ $[M+H]^+$:317.2400. Found: 317.2470.

N-propyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)propan-1-amine (Entry 5, Table 2.19)

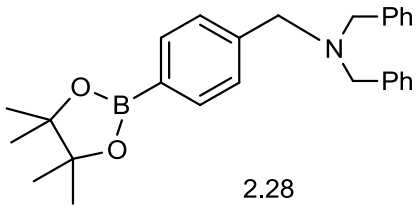


2.27

Following **general procedure VII**, used boronic ester alcohol (0.2354 g, 1 mmol) and dipropylamine (0.13 mL, 1 mmol) to give the title compound as a black oil (0.28 g,

87%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.67 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.27 (2H, d, *J* = 8.0 Hz, Ar**H**), 3.49 (2H, s, PhC$\mathbf{H}_2$N), 2.31-2.26 (4H, m, N(C$\mathbf{H}_2$$CH_2CH_3)_2$), 1.43-1.36 (4H, m, N($CH_2C\mathbf{H}_2$$CH_3)_2$), 1.27 (12H, s, (C$\mathbf{H}_3$)$_2$CC(C$\mathbf{H}_3$)$_2$), 0.77 (6H, t, *J* = 7.3 Hz, N(CH_2CH_2C$\mathbf{H}_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 134.6, 128.2, 83.6, 58.8, 55.9, 24.9, 20.2, 11.9; ESI-MA: Calculated for $C_{19}H_{33}BNO_2$ $[M+H]^+$:318.2604. Found: 318.2699.

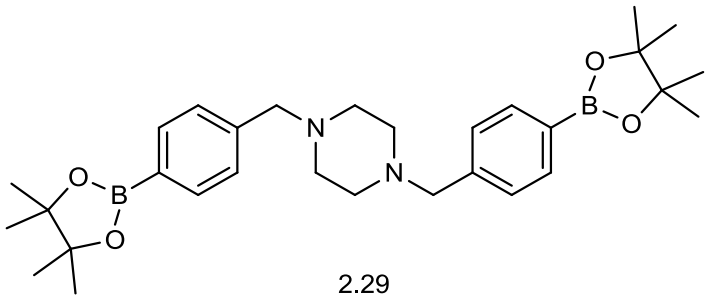
N,N-dibenzyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (Entry 6, Table 2.19)



2.28

Following **general procedure VII**, used boronic ester alcohol (0.2344 g, 1 mmol) and dibenzylamine (0.228 mL, 1 mmol) to give the title compound as a brown oil (0.29 g, 59%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.80 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.47-7.26 (12H, m, Ar**H**), 3.59-3.57 (6H, m, (PhC$\mathbf{H}_2$)$_3$N), 1.36 (12H, s, (C$\mathbf{H}_3$)$_2$CC(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 143.1, 139.5, 134.9, 128.8, 128.7, 128.4, 128.2, 126.9, 83.7, 57.9, 53.2, 24.9; ESI-MA: Calculated for $C_{27}H_{33}BNO_2$ $[M+H]^+$:414.2604. Found: 414.2641.

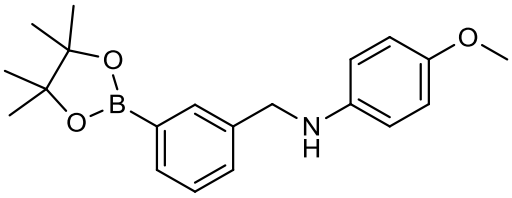
1,4-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine (Entry 7, Table 2.19)



2.29

Following **general procedure VII**, used boronic ester alcohol (0.4698 g, 2 mmol) and piperazine (0.0861 g, 1 mmol) to give the title compound as a orange soild (0.34 g, 65%), m.p.: 122-125 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.68 (4H, d, *J* = 7.9 Hz, Ar**H**), 7.24 (4H, d, *J* = 7.9 Hz, Ar**H**), 3.44 (4H, s, (PhC**H**$_2$N)$_2$), 2.38 (8H, bro, N(C**H**$_2$C**H**$_2$)$_2$N), 1.26 (24H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 141.5, 134.7, 128.9, 128.5, 83.7, 63.1, 53.1, 24.8; ESI-MA: Calculated for $C_{30}H_{45}B_2N_2O_4$ $[M+H]^+$:519.3565. Found: 519.3586.

N-(4-methoxybenzyl)-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (Entry 1, Table 2.18)

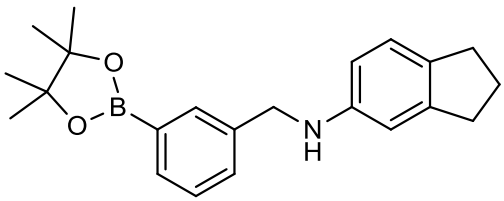


2.41

Following **general procedure VII**, used boronic ester alcohol (0.2339 g, 1 mmol) and p- anisidine (0.1231 g, 1 mmol) to give the title compound as a purple oil (0.22 g, 66%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.81 (1H, s, Ar**H**), 7.72 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.49 (1H, d, *J* = 7.3 Hz, ArH), 7.35 (1H, t, *J* = 7.3 Hz, ArH), 6.77 (2H, d, *J* = 9.0 Hz, ArH), 6.61 (2H, d, *J* = 9.0 Hz, ArH), 4.28 (2H, s, PhC**H**$_2$N), 3.74 (3H, s, OCH_3), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 145.1, 135.6, 134.1, 133.7,

130.6, 128.1, 122.1, 114.9, 114.4, 114.2, 83.8, 55.8, 49.3, 24.9; ESI-MA: Calculated for $C_{20}H_{27}BNO_3$ $[M+H]^+$:340.2084. Found: 340.2089.

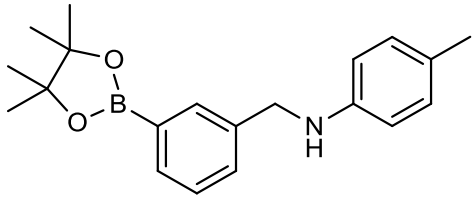
N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-2,3-dihydro-1H-inden-5-amine (Entry 2, Table 2.18)



2.42

Following **general procedure VII**, used boronic ester alcohol (0.2351 g, 1 mmol) and 5-aminoindan (0.1331 g, 1 mmol) to give the title compound as a dark brown oil (0.25 g, 71%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.82 (1H, s, Ar**H**), 7.72 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.50 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.35 (1H, t, *J* = 7.4 Hz, ArH), 7.02 (1H, d, *J* = 8.0 Hz, ArH), 6.55 (1H, s, ArH), 6.46 (1H, d, *J* = 8.0 Hz, ArH), 4.31 (2H, s, PhC**H**$_2$N), 2.84-2.77 (4H, m, Ph(C**H**$_2$)$_2$CH$_2$), 2.05-2.00 (2H, m, Ph(CH$_2$)$_2$C**H**$_2$), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 147.1, 145.4, 138.9, 137.4, 135.7, 133.9, 130.5, 128.2, 124.7, 119.1, 111.3, 109.1, 83.8, 48.9, 32.9, 25.7, 24.9; ESI-MA: Calculated for $C_{22}H_{28}BNNaO_2$ $[M+Na]^+$:372.2111. Found: 372.2114.

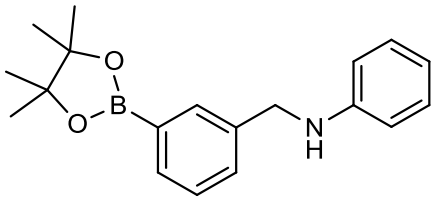
4-methyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)aniline (Entry 3, Table 2.18)



2.43

Following **general procedure VII**, used boronic ester alcohol (0.2341 g, 1 mmol) and p-toluidine (0.1071 g, 1 mmol) to give the title compound as a purple oil (0.20 g, 62%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.82 (1H, s, Ar**H**), 7.72 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.49 (1H, d, *J* = 7.5 Hz, ArH), 7.34 (1H, t, *J* = 7.5 Hz, ArH), 6.98 (2H, d, *J* = 8.1 Hz, ArH), 6.57 (2H, d, *J* = 8.1 Hz, ArH), 4.30 (2H, s, PhC**H**$_2$N), 2.24 (3H, s, $PhCH_3$), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 145.9, 138.8, 133.9, 133.6, 130.5, 129.7, 128.2, 126.7, 120.8, 113.1, 83.8, 48.7, 24.9, 20.4; ESI-MA: Calculated for $C_{20}H_{27}BNO_2$ $[M+H]^+$:324.2135. Found: 324.2166.

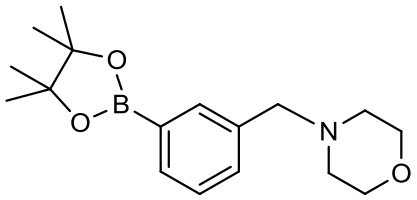
N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)aniline (Entry 4, Table 2.18)



2.44

Following **general procedure VII**, used boronic ester alcohol (0.2374 g, 1 mmol) and aniline (0.129 mL, 1 mmol) to give the title compound as a pale purple oil (0.14 g, 43%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.75 (1H, s, Ar**H**), 7.65 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.41 (1H, d, *J* = 7.5 Hz, ArH), 7.27 (1H, t, *J* = 7.5 Hz, ArH), 7.11-7.06 (2H, m, ArH), 6.63 (1H, t, *J* = 7.4 Hz, ArH), 6.56 (2H, d, *J* = 7.4 Hz, ArH), 4.24 (2H, s, PhC**H**$_2$N), 1.27 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 148.2, 138.6, 133.9, 130.5, 129.2, 128.1, 120.2, 117.5, 112.8, 83.9, 48.3, 24.9; ESI-MA: Calculated for $C_{19}H_{24}BNNaO_2$ $[M+Na]^+$:332.1798. Found: 332.1797.

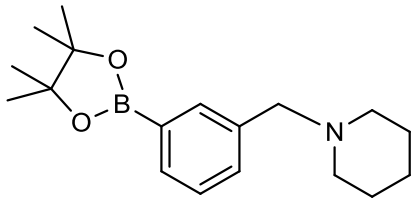
4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine (Entry 1, Table 2.20)



2.9

Following **general procedure VII**, used boronic ester alcohol (0.2346 g, 1 mmol) and morpholine (0.09 mL, 1 mmol) to give the title compound as a dark brown oil (0.24 g, 80%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.65 (1H, s, Ar**H**), 7.64-7.62 (1H, m, Ar**H**), 7.49 (1H, d, *J* = 7.6 Hz, ArH), 7.27 (1H, d, *J* = 7.6 Hz, ArH), 3.63 (4H, t, *J* = 4.6 Hz, $N(CH_2C\mathbf{H}_2)_2O$), 3.43 (2H, s, $PhC\mathbf{H}_2N$), 2.37 (4H, t, *J* = 4.6 Hz, $N(C\mathbf{H}_2CH_2)_2O$), 1.27 (12H, s, $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 136.9, 135.6, 133.7, 132.3, 127.7, 83.8, 67.1, 63.4, 53.6, 24.9; ESI-MA: Calculated for $C_{17}H_{27}BNO_3$ $[M+H]^+$:304.2084. Found: 304.2204.

1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (Entry 2, Table 2.20)

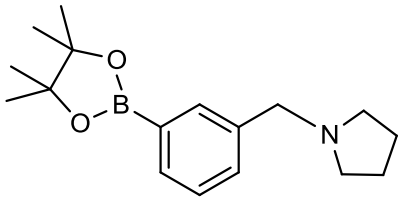


2.30

Following **general procedure VII**, used boronic ester alcohol (0.2347 g, 1 mmol) and piperidine (0.098 mL, 1 mmol) to give the title compound as a black oil (0.24 g, 79%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.70 (1H, s, Ar**H**), 7.69 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.45 (1H, d, *J* = 7.6 Hz, ArH), 7.32 (1H, t, *J* = 7.6 Hz, ArH), 3.47 (2H, s, $PhC\mathbf{H}_2N$), 2.36

(4H, t, *J* = 4.4 Hz, N(C**H**$_2$CH$_2$)$_2$CH$_2$), 1.57 (4H, dt, *J* = 10.8, 5.6 Hz, N(CH$_2$C**H**$_2$)$_2$CH$_2$), 1.42 (2H, dd, *J* = 10.8, 5.6 Hz, N(CH$_2$CH$_2$)$_2$C**H**$_2$), 1.34 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 137.8, 135.7, 133.4, 132.3, 127.5, 83.7, 63.8, 54.4, 25.9, 24.9, 24.4; ESI-MA: Calculated for $C_{18}H_{29}BNO_2$ $[M+H]^+$:302.2291. Found: 302.2295.

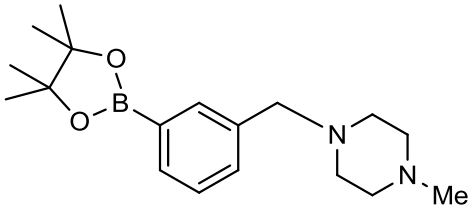
1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pyrrolidine (Entry 3, Table 2.20)



2.31

Following **general procedure VII**, used boronic ester alcohol (0.2354 g, 1 mmol) and pyrrolidine (0.083 mL, 1 mmol) to give the title compound as a dark brown oil (0.22 g, 78%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.74 (1H, s, Ar**H**), 7.70 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.47-7.45 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.31 (1H, t, *J* = 7.4 Hz, Ar**H**), 3.62 (2H, s, PhC**H**$_2$N), 2.52-2.48 (4H, m, N(C**H**$_2$CH$_2$)$_2$), 1.79-1.75 (4H, m, N(CH$_2$C**H**$_2$)$_2$), 1.34 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 138.6, 135.3, 133.4, 132.1, 127.6, 83.7, 60.6, 54.1, 24.9, 23.4; ESI-MA: Calculated for $C_{18}H_{27}BNO_2$ $[M+H]^+$:288.2153. Found: 288.2195.

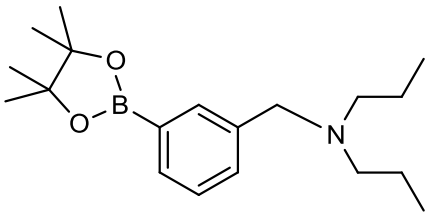
1-methyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine (Entry 4, Table 2.20)



2.23

Following **general procedure VII**, used boronic ester alcohol (0.2348 g, 1 mmol) and 1-methylpiperazine (0.11 mL, 1 mmol) to give the title compound as a brown oil (0.25 g, 80%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.71-7.68 (2H, m, Ar**H**), 7.45 (1H, d, *J* = 7.7 Hz, ArH), 7.32 (1H, t, *J* = 7.7 Hz, ArH), 3.50 (2H, s, PhC**H**$_2$N), 2.45 (8H, bro, N(C**H**$_2$C**H**$_2$)$_2$N), 2.27 (3H, s, NC**H**$_3$), 1.34 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 137.4, 135.6, 133.5, 132.2, 127.6, 83.7, 63.1, 55.1, 53.1, 46.1, 24.9; ESI-MA: Calculated for $C_{18}H_{30}BN_2O_2$ $[M+H]^+$:317.2400. Found: 317.2492.

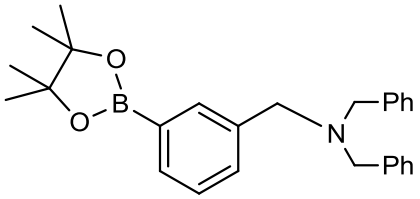
N-propyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)propan-1-amine (Entry 5, Table 2.20)



2.33

Following **general procedure VII**, used boronic ester alcohol (0.2346 g, 1 mmol) and dipropylamine (0.13 mL, 1 mmol) to give the title compound as a yellow oil (0.22 g, 69%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.62 (1H, s, Ar**H**), 7.60 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.43 (1H, d, *J* = 7.9 Hz, ArH), 7.24 (1H, t, *J* = 7.9 Hz, ArH), 3.47 (2H, s, PhC**H**$_2$N), 2.29 (4H, t, *J* = 7.3 Hz, N(C**H**$_2$CH$_2$CH$_3$)$_2$), 1.39 (4H, m, N(CH$_2$C**H**$_2$CH$_3$)$_2$), 1.27 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$), 0.78 (6H, t, *J* = 7.3 Hz, N(CH$_2$CH$_2$C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 135.1, 133.3, 133.1, 131.9, 127.6, 83.7, 58.6, 55.9, 24.9, 20.1, 11.9; ESI-MA: Calculated for $C_{19}H_{33}BNO_2$ $[M+H]^+$:318.2604. Found: 318.2679.

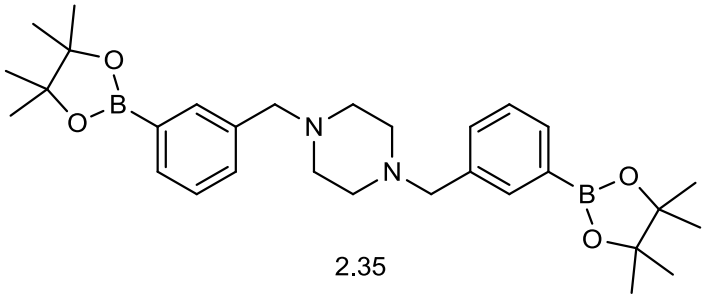
N,N-dibenzyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (Entry 6, Table 2.20)



2.34

Following **general procedure VII**, used boronic ester alcohol (0.2345 g, 1 mmol) and dibenzylamine (0.228 mL, 1 mmol) to give the title compound as a yellow solid (0.27 g, 65%), m.p.: 154-156 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.66 (1H, s, Ar**H**), 7.60 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.53 (1H, d, *J* = 7.3 Hz, ArH), 7.40 (1H, t, *J* = 7.3 Hz, ArH), 7.34-7.20 (10H, m, 2Ar**H**), 3.48 (6H, s, (PhC**H**$_2$)$_3$N), 1.27 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 139.7, 139.6, 135.2, 131.7, 128.8, 128.7, 128.4, 128.2, 126.8, 83.7, 57.9, 24.9; ESI-MA: Calculated for $C_{27}H_{33}BNO_2$ $[M+H]^+$:414.2604. Found: 414.2675.

1,4-bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine (Entry 7, Table 2.20)

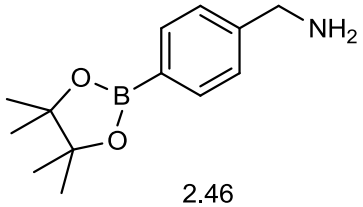


2.35

Following **general procedure VII**, used boronic ester alcohol (0.4709 g, 2 mmol) and piperazine (0.0861 g, 1 mmol) to give the title compound as a brown solid (0.34 g, 65%), m.p.: 175-177 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.64-7.60 (4H, m, Ar**H**), 7.38-7.35 (2H, m, ArH), 7.24 (2H, t, *J* = 7.6 Hz, ArH), 3.43 (4H, s, PhC**H**$_2$N), 2.40 (8H,

bro, N(C**H**$_2$C**H**$_2$)$_2$N), 1.27 (24H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 137.3, 135.6, 133.5, 132.3, 128.9, 127.6, 83.7, 63.1, 53.1, 24.9; ESI-MA: Calculated for $C_{30}H_{45}B_2N_2O_4$ $[M+H]^+$:519.3565. Found: 519.3556.

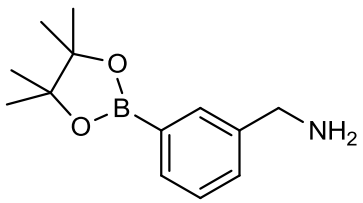
6.3.8 General Procedure VIII for the Preparation of (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine



2.46

(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (0.9 g, 6 mmol) and pinacol (0.83 g, 7 mmol) were mixed in toluene (60 mL). A Dean Stark head was fitted and the reaction was heated under reflux condition for 2 hours. The mixture was allowed to cool to room temperature, and then filtered to get a colourless crystal (1.14 g, 81.4%); m.p.: 254-262 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.84 (2H, d, *J* = 7.7 Hz, Ar**H**), 7.40 (2H, d, *J* = 7.7 Hz, Ar**H**), 4.75 (2H, s, PhC**H**$_2$OH), 1.38 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 137.8, 136.8, 129.6, 85.7, 44.7, 25.6; ESI-MA: Calculated for $C_{13}H_{21}BNO_2$ $[M+H]^+$:234.1665. Found: 234.1691.

6.3.9 General Procedure VIII for the Preparation of (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine

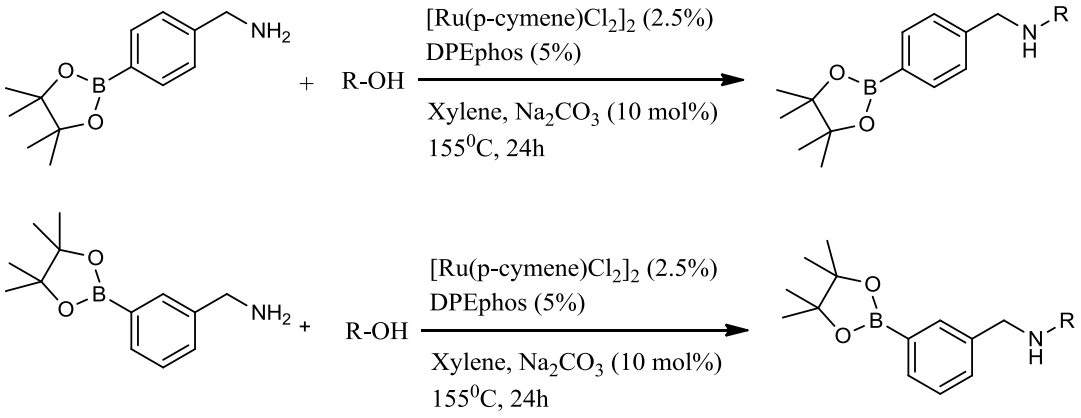


2.50

(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (0.91 g, 6 mmol) and pinacol (0.83 g, 7 mmol) were mixed in toluene (60 mL). A Dean Stark head was

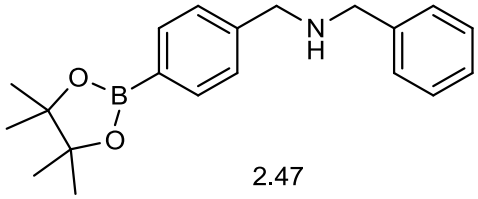
fitted and the reaction was heated under reflux condition for 2 hours. The mixture was allowed to cool to room temperature, and then filtered to Obtain a colourless crystalline product (1.33 g, 95.6%); m.p.: 185-188 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.80 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.78 (1H, s, Ar**H**), 7.69 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.40 (1H, t, *J* = 7.8 Hz, Ar**H**), 4.10 (2H, s, PhC**H**$_2$OH), 1.34 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 136.8, 136.5, 134.2, 133.3, 130.1, 85.7, 44.7, 25.6; ESI-MA: Calculated for $C_{13}H_{21}BNO_2$ $[M+H]^+$:234.1665. Found: 234.1689.

6.3.10 General Procedure IX for the Ruthenium-catalysed N-Alkylation of boronic ester amine with alcohol by borrowing hydrogen



To an oven-dried, nitrogen-purged Radley's carousel tube containing [Ru(*p*-cymene)Cl_2]$_2$ (15.3 mg,0.025 mmol), DPEphos (53.8 mg, 0.05 mmol), Na_2CO_3 (10.6 mg, 0.1 mmol), xylene (2 mL), boronic ester amine (1 mmol) and alcohol (1 mmol). The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature and then increased the temperature to 155 ^{0}C to reflux for 24 hours. The resulting crude compounds were evaporated *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of boronic ester alcohol and amine products in the proton NMR spectrum if the crude reaction mixture. All products were purified by recrystallised using DCM:Hexane (1:20).

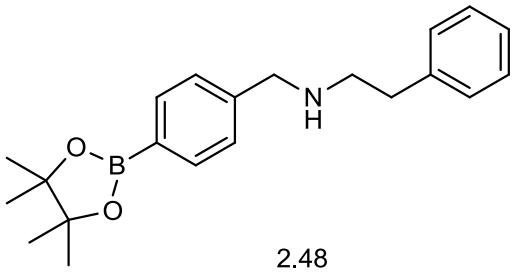
N-benzyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (Entry 1, Table 2.21)



2.47

Following **general procedure IX**, used boronic ester amine (0.2350 g, 1 mmol) and benzylalcohol (0.103 mL, 1 mmol) to give the title compound as a pale red solid (0.19 g, 60%), m.p.: 132-135 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.80 (2H, d, *J* = 8.0 Hz, ArH), 7.48 (4H, dd, *J* = 8.0 Hz, Ar**H**), 7.36 (3H, t, *J* = 8.0 Hz, Ar**H**), 3.84 (4H, s, (PhC**H**$_2$)$_2$NH), 1.29 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 135.4, 130.4, 130.0, 129.6, 129.3, 129.1, 128.5, 83.9, 48.6, 24.8; ESI-MA: Calculated for $C_{20}H_{27}BNO_2$ $[M+H]^+$:324.2135. Found: 324.2185.

2-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)ethanamine (Entry 2, Table 2.21)

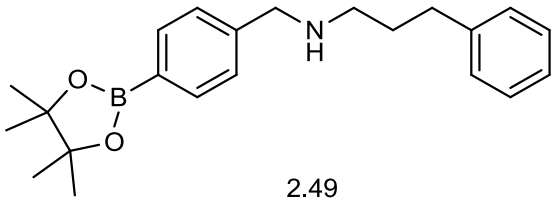


2.48

Following **general procedure IX**, used boronic ester amine (0.2350 g, 1 mmol) and 2-phenylethanol (0.12 mL, 1 mmol) to give the title compound as a dark brown oil (0.20 g, 61%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.85 (2H, d, *J* = 8.1 Hz, ArH), 7.76 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.69 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.29 (3H, m, Ar**H**), 3.84 (2H, s, PhC**H**$_2$NH), 3.03 (2H, t, *J* = 7.5 Hz, NHC**H**$_2$CH$_2$Ph), 2.88 (2H, d, *J* = 7.5 Hz, NHCH$_2$C**H**$_2$Ph), 1.34 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 139.7, 134.9, 129.1, 128.7, 128.5, 128.3, 127.5, 127.2, 83.7, 63.3, 50.2, 36.1, 24.9; ESI-MA:

Calculated for $C_{21}H_{29}BNO_2$ $[M+H]^+$:338.2291. Found: 338.2293.

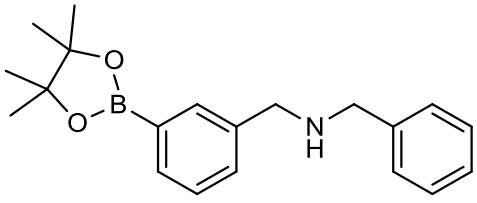
3-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)propan-1-amine (Entry 3, Table 2.21)



2.49

Following **general procedure IX**, used boronic ester amine (0.2350 g, 1 mmol) and 3-phenyl-1-propanol (0.135 mL, 1 mmol) to give the title compound as a green solid (0.23 g, 64%), m.p.: 188-190 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ7.73 (2H, d, *J* = 7.9 Hz, ArH), 7.45 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.13-7.11 (2H, m, Ar**H**), 7.08-7.06 (1H, m, Ar**H**), 7.03-7.00 (2H, m, Ar**H**), 3.88 (2H, s, PhC**H**$_2$NH), 2.64 (2H, t, *J* = 7.4 Hz, NHC**H**$_2$CH$_2$CH$_2$Ph), 2.52 (2H, t, *J* = 7.4 Hz, NHCH$_2$CH$_2$C**H**$_2$Ph), 2.11-2.03 (2H, dd, *J* = 13.7, 6.0 Hz, NHCH$_2$C**H**$_2$CH$_2$Ph), 1.22 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ 144.9, 139.8, 135.4, 129.6, 128.5, 128.3, 126.2, 83.9, 51.7, 45.2, 27.6, 27.1, 24.8; ESI-MA: Calculated for $C_{22}H_{31}BNO_2$ $[M+H]^+$:352.2448. Found: 352.2451.

N-benzyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (Entry 1, Table 2.22)

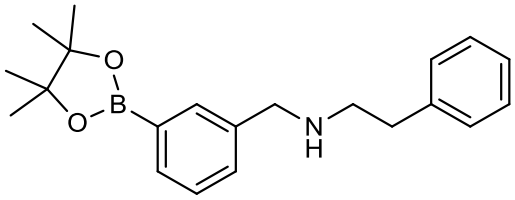


2.51

Following **general procedure IX**, used boronic ester amine (0.2361 g, 1 mmol) and benzylalcohol (0.103 mL, 1 mmol) to give the title compound as a brown liquid (0.20

g, 61%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.74 (1H, d, *J* = 7.7 Hz, ArH), 7.65 (2H, t, *J* = 7.6 Hz, Ar**H**), 7.59 (1H, s, Ar**H**), 7.42 (2H, dd, *J* = 6.4, 2.8 Hz, Ar**H**), 7.29-7.23 (3H m, Ar**H**), 3.89 (4H, d, *J* = 7.6 Hz, (PhC**H**$_2$)$_2$NH), 1.21 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ 137.6, 137.1, 134.3, 133.3, 132.8, 131.4, 130.7, 130.1, 129.8, 128.4, 85.8, 52.7, 52.5 25.7; ESI-MA: Calculated for $C_{20}H_{27}BNO_2$ $[M+H]^+$:324.2135. Found: 324.2199.

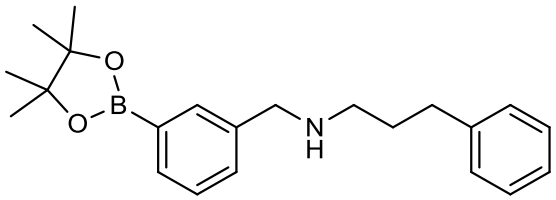
2-phenyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)ethanamine (Entry 2, Table 2.22)



2.52

Following **general procedure IX**, used boronic ester amine (0.2350 g, 1 mmol) and 2-phenylethanol (0.12 mL, 1 mmol) to give the title compound as a yellow solid (0.18 g, 53%), M.P.: 90-92 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.07 (1H, s, Ar**H**), 7.86 (1H, t, *J* = 7.2 Hz, Ar**H**), 7.70 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.42 (3H, t, *J* = 7.5 Hz, Ar**H**), 7.28 (2H, d, *J* = 7.2 Hz, Ar**H**), 3.83 (2H, s, PhC**H**$_2$NH), 3.02 (2H, t, *J* = 7.6 Hz, NHC**H**$_2$CH$_2$Ph), 2.89 (2H, t, *J* = 7.6 Hz, NHCH$_2$C**H**$_2$Ph), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ 139.9, 136.9, 135.5, 134.6, 131.2, 130.2, 129.1, 128.7, 126.3, 126.1, 83.8, 63.3, 53.6, 37.5, 24.9; ESI-MA: Calculated for $C_{21}H_{29}BNO_2$ $[M+H]^+$:338.2291. Found: 338.2307.

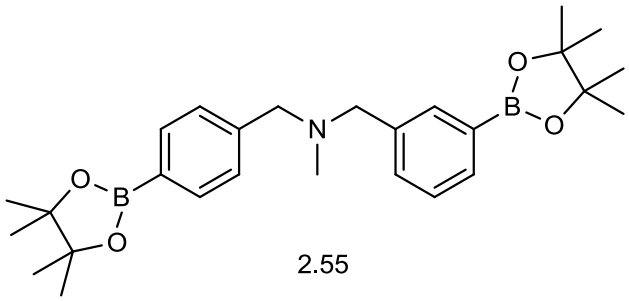
3-phenyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)propan-1-amine (Entry 3, Table 2.22)



2.53

Following **general procedure IX**, used boronic ester amine (0.2347 g, 1 mmol) and 3-phenyl-1-propanol (0.135 mL, 1 mmol) to give the title compound as a brown oil (0.21 g, 60%), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.75-7.70 (3H, m, ArH), 7.46-7.28 (6H, m, ArH), 3.79 (2H, s, PhC**H**$_2$NH), 2.67-2.63 (4H, m, NHC**H**$_2$CH$_2$C**H**$_2$Ph), 1.90-1.80 (2H, m, NHCH$_2$C**H**$_2$CH$_2$Ph), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ 134.6, 133.5, 131.3, 128.5, 128.4, 128.3, 127.9, 126.1, 125.7, 83.8, 53.8, 48.5, 33.6, 33.2, 24.9; ESI-MA: Calculated for $C_{22}H_{31}BNO_2$ $[M+H]^+$:352.2448. Found: 352.2464.

6.3.11 General Procedure X for the Preparation of N-methyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (Entry 1, Table 2.23)

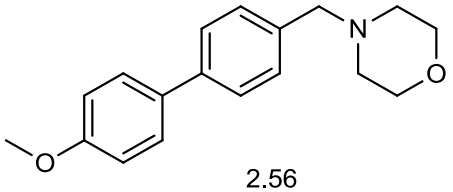


2.55

(4-formylphenyl)boronic acid (1.49 g, 10 mmol) and pinacol (1.41 g, 12 mmol) were mixed in toluene (100 mL). A Dean-Stark head was fitted and the reaction was heated under reflux condition for 2 hours. The mixture was allowed to cool to room temperature, and then washed with water (4 x 100 mL). The organic layer was condensed under reduced pressure and DCM was added. This was washed with water (3 x 100 mL) and dried over sodium sulphate and filtered. The solvents were again removed under reduced pressure to obtain the boronic ester aldehydes. These boronic ester aldehydes (2.23 g, 9.6 mmol) was dissolved in MeOH (100 mL) and $MeNH_2$ (40% in H_2O, 0.69 mL) was added. The reaction mixture was stirred in 0°C for 2 hours under N_2 atmosphere. After that, $NaBH_4$ (0.76 g) was added slowly and the mixture stirred in 0°C for 30 mins. The all reaction mixture was stirred at room temperature for 48 hours. The solvents were removed under reduced pressure and DCM was added. This was washed with water (5 x 100 mL) and dried over sodium sulphate and filtered. The solvent were again removed under reduced pressure to obtain the product amine (N-methyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine). To an oven-dried, nitrogen-purged Radley's carousel tube containing the product amine from last step (0.2488 g, 1 mmol) and meta-boronic ester alcohol (0.2346 g, 1 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (15.3 mg, 0.02 5mmol), DPEphos (53.8 mg, 0.05 mmol), Na_2CO_3 (10.6 mg, 0.1 mmol) and xylene (2 mL). The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature and then increased the temperature to 155^0C to reflux for 24 hours. The resulting crude compounds were evaporated *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of boronic ester alcohol and amine products in the proton NMR spectrum if the crude reaction mixture. The title compound was purify by recrystallised with DCM:Hexane (1:20) and give a yellow solid (0.38 g, 82%), m.p.: 298-300 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.72-7.63 (4H, m, ArH), 7.42 (2H, dd, *J* = 7.4 Hz, Ar**H**), 7.31 (2H, d, *J* = 7.3 Hz, Ar**H**), 3.45 (4H, s, $(PhC\mathbf{H}_2)_2NCH_3$), 2.08 (3H, s, $(PhCH_2)_2NC\mathbf{H}_3$), 1.27 (24H, s, 2 x $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ 135.3, 134.7, 134.1, 133.5, 133.3, 132.0, 130.0, 128.4, 128.1, 127.7, 83.7, 65.3, 61.8, 42.2, 24.9; ESI-MA: Calculated for

$C_{27}H_{39}B_2NNaO_4$ $[M+Na]^+$:486.2963. Found: 486.2954.

6.3.12 General Procedure XI for the Preparation of 4-((4'-Methoxy-[1,1'-biphenyl]-4-yl)methyl)morpholine[115]

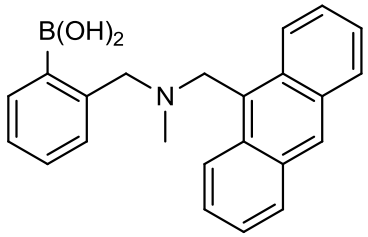


2.56

To an oven-dried, nitrogen-purged Radley's carousel tube containing $Pd(PPh_3)_4$ (115.5 mg, 0.1 mmol), 4-Iodoanisole (0.234g, 1mmol), 4-(4-Morpholinomethyl)phenylboronic acid pinacol ester (0.3032g, 1mmol), xylene (1.5 mL) and 2M sodium carbonate (0.5ml), The reaction mixture was heated at 155 ^{0}C for 12h, cooled down to room temperature. The solvent was removed under reduced pressure. The product was purified by recrystallised using DCM:methanol(100:0.5). Finally, we get the title compound as a yellow solid (0.1882 g, 67%), m.p.: 62-65 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 7.61-7.36 (8H, m, Ar**H**), 3.85 (3H, s, ArOC**H**$_3$), 3.74 (4H, t, *J* = 7.9 Hz, N(CH_2C**H**$_2$)$_2$O), 3.54 (2H, s, ArC**H**$_2$N) 2.49 (4H, t, *J* = 7.9 Hz, N(C**H**$_2$$CH_2$)$_2$O); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ 159.1, 133.4, 129.7, 128.7, 128.0, 127.0, 126.6, 114.2, 66.9, 63.1, 55.3, 53.6; ESI-MA: Calculated for $C_{18}H_{22}NO_2$ $[M+H]^+$:284.1651. Found: 284.1696.

6.4 Experimental Procedures for Chapter 3

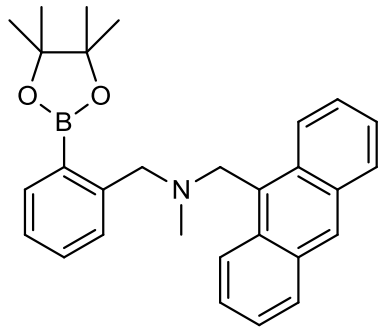
6.4.1 General Procedure I for the Preparation of (2-(((anthracen-9-ylmethyl)(methyl)amino)methyl)phenyl)boronic acid



3.2

To an oven-dried, nitrogen-purged Radley's carousel tube containing K_2CO_3 (27.6 mg, 0.2 mmol), methanol (4 mL), boronic acid aldehyde (4 mmol) and 9-(Methylaminomethyl)anthracene (2 mmol). The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for overnight. After that, $NaBH_4$ (151.3mg, 4mmol) was dissolved in 6ml methanol and added into the carousel tube. The mixture was stirring for 1 hour and the resulting crude compounds were evaporated in *vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of products in the proton NMR spectrum. The product was purified by recrystallised using DCM:methanol(100:1). Finally, we get the title compound as a yellow solid (0.411 g, 58%), m.p.:145-148 °C, ^{1}H NMR (300 MHz, MeOD, 25 °C): δ 8.47 (1H, s, Ar**H**), 7.98 (4H, dd, *J* = 20.7, 8.6 Hz, Ar**H**), 7.62 (2H, d, *J* = 6.6 Hz, Ar**H**), 7.41-7.16 (7H, m, Ar**H**), 4.89 (2H, s, PhC**H**$_2$NCH$_3$CH$_2$Ar), 4,31 (2H, s, PhCH$_2$NCH$_3$C**H**$_2$Ar), 2.31 (3H, s, PhCH$_2$NC**H**$_3$CH$_2$Ar); ^{13}C NMR (75.5 MHz, MeOD, 25°C): δ 135.9, 133.1, 133.0, 132.3, 131.6, 130.8, 129.4, 128.6, 128.3, 126.7, 125.1, 64.7, 40.4; ESI-MA: Calculated for $C_{23}H_{22}BNNaO_2$ $[M+Na]^+$:378.1641. Found: 378.1640.

6.4.2 General Procedure II for the Preparation of 1-(anthracen-9-yl)-N-methyl-N-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)methanamine

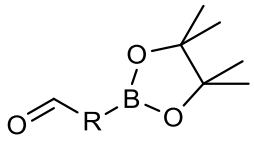


3.5

To an oven-dried, nitrogen-purged Radley's carousel tube containing [Ru(*p*-cymene)Cl_2]$_2$ (15.3 mg, 0.025 mmol), DPEphos (53.8 mg, 0.05 mmol), Na_2CO_3 (10.6 mg, 0.1 mmol), xylene (2 mL), 9-(Methylaminomethyl)anthracene (1 mmol) and boronic ester alcohol (1 mmol). The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature and then increased the temperature to 155 ^{0}C to reflux for 24 hours. The resulting crude compounds were evaporated in *vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of boronic ester alcohol and amine products in the proton NMR spectrum if the crude reaction mixture. The product was purified by recrystallised using DCM:methanol (100:1) to give the title compound as a orange yellow solid (0.25 g, 84 %), m.p.: 113-115 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 8.37-8.30 (2H, m, Ar**H**), 7.95 (1H, d, *J* = 2.4 Hz, Ar**H**), 7.85 (1H, d, *J* = 7.0 Hz, Ar**H**), 7.47-7.40 (9H, m, Ar**H**), 4.38 (2H, s, PhC**H**$_2$NCH$_3$CH$_2$Ar), 4.00 (2H, s, PhCH$_2$NCH$_3$C**H**$_2$Ar), 2.22 (3H, s, PhCH$_2$NC**H**$_3$CH$_2$Ar), 1.28 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ 135.3, 131.4, 130.6, 130.3, 129.7, 129.2, 128.8, 127.2, 126.4, 125.9, 125.4, 124.9, 124.7, 83.4, 62.2, 52.1, 42.5, 24.9; ESI-MA: Calculated for $C_{29}H_{33}BNO_2$ $[M+H]^+$:438.2604. Found: 438.2621

6.5 Experimental Procedures for Chapter 4

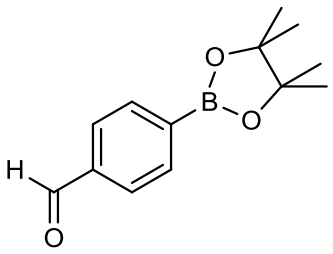
6.5.1 General Procedure I for the Preparation of Boronic acid ester



(R = phenyl, furan or thiophene)

Bornic acid aldehyde (30 mmol) and pinacol (4.13 g, 35 mmol) were mixed in toluene (300 mL) in a round-bottomed flask. A Dean stark head was fitted and the reaction was heated under reflux condition for 2 hours. The mixture was allowed to cool to room temperature, and then washed with water (3 x 150 mL). The organic layer was condensed under reduced pressure and DCM (100mL) was added. This was washed with water (3 x 150 mL), dried over $MgSO_4$ and filtered. The solvents were again removed under reduced pressure to yield compound for further reaction. The resulting aldehydes were analysed by their 1H and 13C NMR spectra and mass spectrometry data and used without further purification.

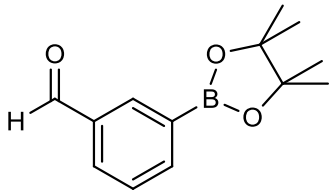
(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (Entry 1, Table 4.1)



4.1

Following **general procedure I**, used (4-(Hydroxymethyl)phenyl)boronic acid (4.57 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a colourless solid (6.45 g, 92.7%); m.p.: 55-58 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 10.04 (1H, s, **H**C=O), 7.96 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.86 (2H, d, *J* = 7.6 Hz, PhC**H**$_2$OH), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 192.7, 138.1, 135.2, 128.7, 84.3, 24.9; ESI-MA: Calculated for $C_{13}H_{18}BO_3$ $[M+H]^+$:233.1349. Found: 233.1367.

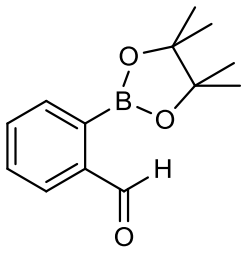
(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (Entry 2, Table 4.1)



4.2

Following **general procedure I**, used (3-(Hydroxymethyl)phenyl)boronic acid (4.57 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a colourless solid (6.21 g, 89.2%); m.p.: 50-54 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 9.91 (1H, s, **H**C=O), 8.18 (1H, s, Ar**H**), 7.93 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.84 (1H, d, *J* = 7.5 Hz, ArH), 7.39 (1H, t, *J* = 7.5 Hz, ArH), 1.23 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 140.1, 134.1, 133.3, 130.1, 128.1, 83.9, 65.3, 24.8; ESI-MA: Calculated for $C_{13}H_{17}BNaO_3$ $[M+Na]^+$: 255.1168. Found: 255.1175.

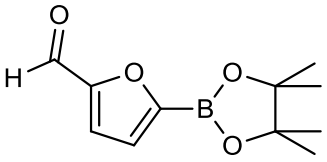
2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (Entry 3, Table 4.1)



4.3

Following **general procedure I**, used (2-(Hydroxymethyl)phenyl)boronic acid (4.57 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a red oil (5.46 g, 78.6%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 10.53 (1H, s, **H**C=O), 7.95 (1H, d, *J* = 6.6 Hz, Ar**H**), 7.84 (1H, d, *J* = 6.6 Hz, Ar**H**), 7.60 – 7.51 (2H, m, ArH), 1.38 (12H, s, $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 194.6, 141.2, 135.5, 133.0, 130.7, 127.9, 84.4, 24.9; ESI-MA: Calculated for $C_{13}H_{18}BO_3$ $[M+H]^+$:233.1349. Found: 233.1353.

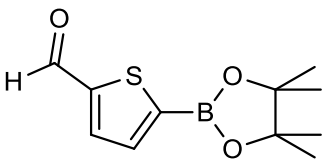
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carbaldehyde (Entry 4, Table 4.1)



4.4

Following **general procedure I**, used (5-formylfuran-2-yl)boronic acid (4.197 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a light yellow solid (5.92 g, 88.9%); m.p.: 52-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 9.79 (1H, s, **H**C=O), 7.23 (1H, d, *J* = 3.6 Hz, furyl), 7.12 (1H, d, *J* = 3.6 Hz, furyl), 1.34 (12H, s, $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 179.3, 156.2, 124.4, 118.4, 85.0, 24.7; ESI-MA: Calculated for $C_{11}H_{16}BO_4$ $[M+H]^+$:223.1142. Found: 223.1138; IR: v (cm-1) = 1723.28 (C=O stretch)

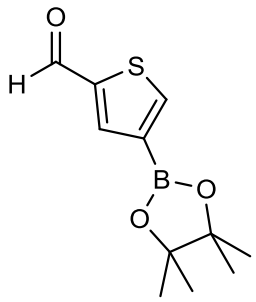
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carbaldehyde (Entry 5, Table 4.1)



4.5

Following **general procedure I**, used (5-formylthiophen-2-yl)boronic acid (4.671 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a yellow solid (6.42 g, 89.9%); m.p.: 62-64 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 9.91 (1H, s, **H**C=O), 7.73 (1H, d, *J* = 3.7 Hz, thiophene), 7.58 (1H, d, *J* = 3.7 Hz, thiophene), 1.29 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 183.1, 148.9, 137.2, 136.1, 84.8, 24.8; ESI-MA: Calculated for $C_{11}H_{15}BNaO_3S$ $[M+Na]^+$:261.0733. Found: 261.0749; IR: v (cm-1) = 1742.43 (C=O stretch)

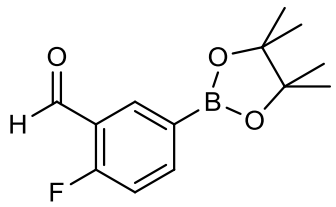
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-3-carbaldehyde (Entry 6, Table 4.1)



4.6

Following **general procedure I**, used (4-formylthiophen-2-yl)boronic acid (4.671 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a green solid (5.89 g, 82.1%); m.p.: 88-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 9.91 (1H, s, **H**C=O), 8.22 (1H, s, thiophene), 8.03 (1H, s, thiophene), 1.31 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 183.2, 145.1, 142.2, 128.2, 84.2, 24.8; ESI-MA: Calculated for $C_{11}H_{15}BNaO_3S$ $[M+Na]^+$:261.0733. Found: 261.0744; IR: v (cm-1) = 1738.33 (C=O stretch)

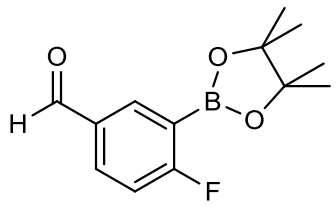
2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (Entry 7, Table 4.1)



4.7

Following **general procedure I**, used (4-fluoro-3-formylphenyl)boronic acid (5.026 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a colourless solid (6.41 g, 85.5%); m.p.: 70-72 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 10.35 (1H, s, **H**C=O), 8.33 (1H, dd, *J* = 7.5, 1.7 Hz Ar**H**), 8.06-7.99 (1H, m, Ar**H**), 7.16 (1H, dd, *J* = 10.6, 8.3 Hz Ar**H**), 1.34 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 187.3 (d, *J* = 6.1 Hz), 166.4 (d, *J* = 263.1 Hz), 142.7, 136.4 (d, *J* = 2.2 Hz), 123.6, 116.1 (d, *J* = 19.7 Hz), 84.3, 24.9; ESI-MA: Calculated for $C_{13}H_{17}BFO_3$ $[M+H]^+$:251.1255. Found: 251.1247; IR: v (cm-1) = 1736.48 (C=O stretch)

4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (Entry 8, Table 4.1)

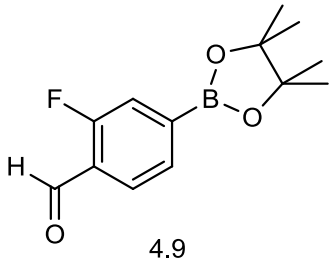


4.8

Following **general procedure I**, used (2-fluoro-5-formylphenyl)boronic acid (5.011 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a colourless solid (6.31 g, 84.3%); m.p.: 78-81 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 9.91 (1H, s, **H**C=O), 8.22 (1H, dd, *J* = 5.7, 2.2 Hz Ar**H**), 8.00-7.88 (1H, m, Ar**H**), 7.11 (1H, t, *J* = 8.6

Hz Ar**H**), 1.31 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 190.7, 170.7 (d, *J* = 261.7 Hz), 140.5 (d, *J* = 10.2 Hz), 134.1 (d, *J* = 10.7 Hz), 132.5 (d, *J* = 2.6 Hz), 129.0, 116.7 (d, *J* = 25.3 Hz), 84.4, 24.8; ESI-MA: Calculated for $C_{13}H_{17}BFO_3$ $[M+H]^+$:251.1255. Found: 251.1273; IR: v (cm-1) = 1727.12 (C=O stretch)

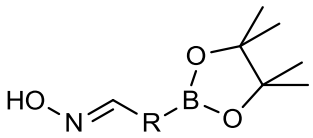
2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (Entry 9, Table 4.1)



4.9

Following **general procedure I**, used (3-fluoro-4-formylphenyl)boronic acid (5.013 g, 30 mmol) and pinacol (4.13 g, 35 mmol) to give the title compound as a colourless solid (6.72 g, 87.1%); m.p.: 75-77 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 9.98 (1H, s, **H**C=O), 7.89 (1H, dd, *J* = 7.5, 5.6 Hz Ar**H**), 7.63 (1H, dd, *J* = 7.5, 1.3 Hz Ar**H**), 7.50 (1H, dd, *J* = 8.9, 1.2 Hz Ar**H**), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 191.1 (d, *J* = 2.1 Hz), 167.2 (d, *J* = 253.7 Hz), 140.4 (d, *J* = 7.1 Hz), 137.7 (d, *J* = 7.9 Hz), 128.5 (d, *J* = 60.9 Hz), 124.9 (d, *J* = 3.2 Hz), 115.4 (d, *J* = 24.9 Hz), 84.4, 24.8; ESI-MA: Calculated for $C_{13}H_{16}BFNaO_3$ $[M+Na]^+$:273.1074. Found: 273.1068; IR: v (cm-1) = 1740.88 (C=O stretch)

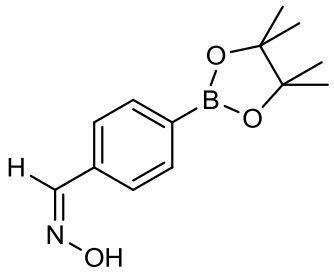
6.5.2 General Procedure II for the Preparation of Boronic aldoxime



(R = phenyl, furan or thiophene)

To a stirred solution of hydroxylamine hydrochloride (2.78g, 40 mmol) in ethanol/water (5:1) (60 mL) was added the appropriate aldehyde (20 mmol) at 0 ^{o}C. Sodium acetate (4.92g, 60 mmol) was added slowly and the reaction mixture was allowed to warm to room temperature and left stirring for 2 – 3 hours. Ethanol was removed from the solution, then 30 mL water was added and the product was extracted into dichloromethane (2 x 60 mL). The combined organic extracts were dried over magnesium sulphate and the solvent removed in vacuo. The resulting aldoximes were analysed by their 1H and 13C NMR spectra and mass spectrometry data and purification by recrystallization.

(Z)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde oxime (Entry 1, Table 4.2)

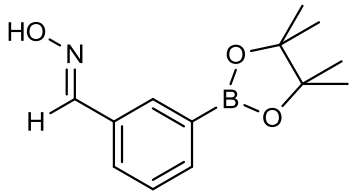


4.10

Following **general procedure II**, used 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (4.64 g, 20 mmol) to give the title compound as a colourless solid (4.46 g, 90.3%); m.p.: 120-122 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.16 (1H, s,

PhC**H**NOH), 7.83 (2H, d, *J* = 8.2 Hz ArH), 7.58 (2H, d, *J* = 8.2 Hz ArH), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 150.4, 135.1, 134.4, 126.2, 84.1, 24.9; ESI-MA: Calculated for $C_{13}H_{17}BNO_3^-$ [M-H]:246.1307. Found: 246.1298.

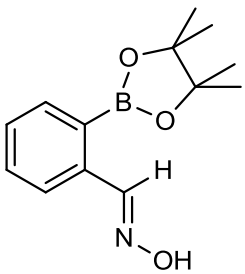
(E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde oxime (Entry 2, Table 4.2)



4.11

Following **general procedure II**, used 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (4.64 g, 20 mmol) to give the title compound as a colourless solid (4.33 g, 87.6%); m.p.: 105-108 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.09 (1H, s, PhC**H**NOH), 7.88 (1H, s, ArH), 7.77 (1H, d, *J* = 7.6 Hz, ArH), 7.67 (1H, d, *J* = 7.6 Hz, ArH), 7.33 (1H, t, *J* = 7.6 Hz, ArH), 1.28 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 150.3, 136.4, 134.1, 131.3, 129.1, 128.2, 84.1, 24.9; ESI-MA: Calculated for $C_{13}H_{19}BNO_3$ $[M+H]^+$:248.1458. Found: 248.1456.

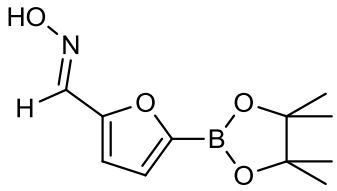
(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde oxime (Entry 3, Table 4.2)



4.12

Following **general procedure II**, used 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (4.64 g, 20 mmol) to give the title compound as a red oil (3.32 g, 67.2%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.34 (1H, s, PhC**H**NOH), 8.02 (1H, d, *J* = 7.0 Hz, ArH), 7.71-7.61 (2H, m, ArH), 7.51 (1H, d, *J* = 7.0 Hz, ArH), 1.18 (12H, s, $(CH_3)_2CC(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 150.5, 135.8, 133.4, 132.1, 131.6, 128.2, 127.1, 84.8, 24.8; ESI-MA: Calculated for $C_{13}H_{18}BNNaO_3$ $[M+Na]^+$:270.1277. Found: 270.1290.

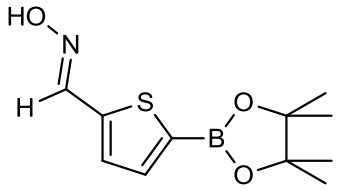
(Z)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carbaldehyde oxime (Entry 4, Table 4.2)



4.13

Following **general procedure II**, used 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) furan-2-carbaldehyde (4.44 g, 20 mmol) to give the title compound as a orange oil (4.08 g, 86.1%). The product was observed as 2 rotamers in its NMR spectra. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.03 (1H, s, **H**CNOH), 7.30 (1H, (major rotamer), d, *J* = 3.5 Hz, furyl), 7.09 (1H, (minor rotamer), d, *J* = 3.5 Hz, furyl), 7.02(1H, (major rotamer), d, *J* = 3.5 Hz, furyl), 6.66 (1H, (minor rotamer), d, *J* = 3.5 Hz, furyl), 1.29 (12H, (major rotamer), s, $(CH_3)_2CC(CH_3)_2$), 1.28 (12H, (minor rotamer), s, $(CH_3)_2CC(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 151.6, 140.7, 125.2, 118.3, 111.3, 84.7, 24.7; ESI-MA: Calculated for $C_{11}H_{16}BNNaO_4$ $[M+Na]^+$:260.1070. Found: 260.1118.

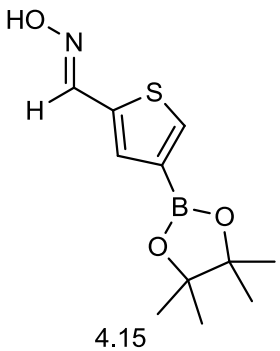
(E)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carbaldehyde oxime (Entry 5, Table 4.2)



4.14

Following **general procedure II**, used 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) thiophene-2-carbaldehyde (4.76 g, 20 mmol) to give the title compound as a yellow solid (4.17 g, 82.4%); m.p.: 144-146 °C; The product was observed as 2 rotamers in its NMR spectra. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.22 (1H, s, **H**CNOH), 7.52 (1H, (major rotamer), d, *J* = 3.7 Hz, thiophene), 7.48 (1H, (minor rotamer), d, *J* = 3.6 Hz, thiophene), 7.38 (1H, (major rotamer) d, *J* = 3.7 Hz, thiophene), 7.19 (1H, (minor rotamer), d, *J* = 3.6 Hz, thiophene), 1.30 (12H, (major rotamer) s, $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$), 1.28 (12H, (minor rotamer), s, $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 144.7, 137.2, 135.9, 132.7, 130.2, 84.5, 24.7; ESI-MA: Calculated for $C_{11}H_{17}BNO_3S$ $[M+H]^+$:254.1022. Found: 254.1039.

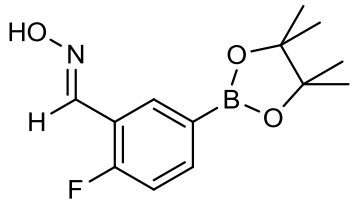
(E)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-3-carbaldehyde oxime (Entry 6, Table 4.2)



4.15

Following **general procedure II**, used 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) thiophene-3-carbaldehyde (4.76 g, 20 mmol) to give the title compound as a yellow solid (3.91 g, 77.3%); m.p.: 117-120 °C; The product was observed as 2 rotamers in its NMR spectra. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.30 (1H, (major rotamer), s, **H**CNOH), 8.15 (1H, (minor rotamer), s, **H**CNOH), 7.92 (1H, (major rotamer), s, thiophene), 7.76 (1H, (minor rotamer), s, thiophene), 7.71 (1H, (major rotamer), s, thiophene), 7.49 (1H, (minor rotamer), s, thiophene), 1.35 (12H, (major rotamer), s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$), 1.34 (12H, (minor rotamer), s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 144.8, 142.7(major rotamer), 141.2(minor rotamer), 138.8(major rotamer), 137.5(minor rotamer), 136.0(major rotamer), 134.9(minor rotamer), 131.3, 84.1, 24.8; ESI-MA: Calculated for $C_{11}H_{17}BNO_3S$ $[M+H]^+$:254.1022. Found: 254.1032.

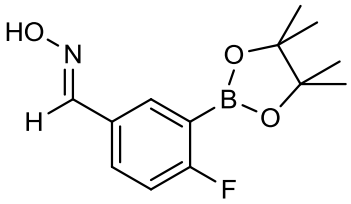
(E)-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde oxime (Entry 7, Table 4.2)



4.16

Following **general procedure II**, used 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (5.00 g, 20 mmol) to give the title compound as a colourless solid (4.42 g, 83.4%); m.p.: 159-161 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.28 (1H, s, **H**CNOH), 8.12 (1H, d, *J* = 6.1 Hz, Ar**H**), 7.78-7.71 (1H, m, Ar**H**), 7.02 (1H, dd, *J* = 10.6, 8.3 Hz, Ar**H**), 1.27 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 162.5 (d, *J* = 256.9 Hz), 144.5 (d, *J* = 3.0 Hz), 138.1 (d, *J* = 8.9 Hz), 134.5 (d, *J* = 3.2 Hz), 119.5, 115.6 (d, *J* = 20.3 Hz), 84.2, 24.8; ESI-MA: Calculated for $C_{13}H_{18}BFNO_3$ $[M+H]^+$:266.1364. Found: 266.1365.

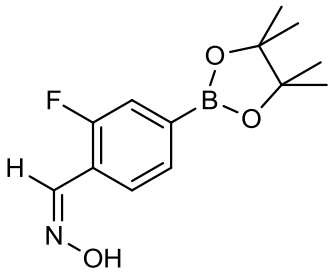
(E)-4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde oxime (Entry 8, Table 4.2)



4.17

Following **general procedure II**, used 4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (5.00 g, 20 mmol) to give the title compound as a colourless solid (4.28 g, 80.8%); m.p.: 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.02 (1H, s, **H**CNOH), 7.77 (1H, d, *J* = 3.4 Hz, Ar**H**), 7.68-7.57 (1H, m, Ar**H**), 6.93 (1H, t, *J* = 8.7 Hz, Ar**H**), 1.22 (12H, s, $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 166.3 (d, *J* = 255.3 Hz), 149.0, 136.5 (d, *J* = 8.6 Hz), 131.3 (d, *J* = 9.3 Hz), 127.9 (d, *J* = 3.4 Hz), 116.1 (d, *J* = 25.0 Hz), 84.3, 24.7; ESI-MA: Calculated for $C_{13}H_{18}BFNO_3$ $[M+H]^+$:266.1364. Found: 266.1360.

(Z)-2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde oxime (Entry 9, Table 4.2)



4.18

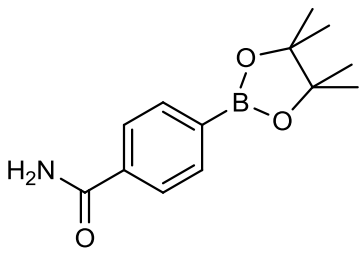
Following **general procedure II**, used 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (5.00 g, 20 mmol) to give the title compound as a colourless solid (4.16 g, 78.5%); m.p.: 155-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ

8.11 (1H, s, **H**CNOH), 7.75 (1H, dd, *J* = 7.6, 6.2 Hz, Ar**H**), 7.29 (2H, dd, *J* = 13.7, 8.8 Hz, Ar**H**), 1.37 (12H, s, $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ167.7 (d, *J* = 251.3 Hz), 149.2 (d, *J* = 2.9 Hz), 137.3 (d, *J* = 8.5 Hz), 137.1 (d, *J* = 8.9 Hz), 122.4 (d, *J* = 3.0 Hz), 113.2 (d, *J* = 25.9 Hz), 84.2, 24.8; ESI-MA: Calculated for $C_{13}H_{17}BFNNaO_3$ $[M+Na]^+$:288.1183. Found: 288.1197.

6.5.3 General Procedure III for the Preparation of Primary boronic amide from aldehyde

To an oven dried Schlenk tube was added the appropriate catalyst followed by hydroxylamine hydrochloride (0.2779 g, 4 mmol) and sodium hydrogen carbonate (0.336 g, 4 mmol), then boronic aldehyde (2 mmol). $Cu(OAc)_2$ (0.0182 g, 5 mol%) was added and PhMe (2 mL) was added to the tube, which was then sealed and the reaction mixture allowed to stir at room temperature for 10 minutes before being heated at reflux. The resulting reaction mixture was allowed to cool and then methanol (3.0 mL) was added. The crude reaction mixture was filtered through a short plug of celite (eluting with dichloromethane) and concentrated *in vacuo*. The resulting amides were analysed by their ^1H NMR, ^{13}C NMR and mass spectrometry data. All compounds were purify by column chromatography with DCM:MeOH (98:2).

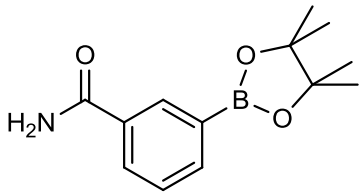
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Entry 1, Table 4.10)



4.19

Following **general procedure III**, used 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (0.46 g, 2 mmol) to give the title compound as a colourless solid (0.41 g, 83.2%); m.p.: 186-188 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.79 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.72 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.38 (2H, Bro, PhCON**H**$_2$), 1.27 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 169.8, 135.6, 134.9, 126.5, 84.2, 24.9; ESI-MA: Calculated for $C_{13}H_{19}BNO_3$ $[M+H]^+$:248.1458. Found: 248.1453.

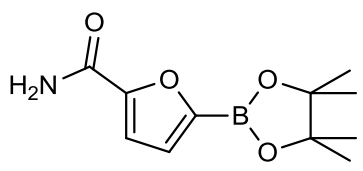
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Entry 2, Table 4.10)



4.20

Following **general procedure III**, used 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (0.46 g, 2 mmol) to give the title compound as a colourless solid (0.39 g, 79.4%); m.p.: 192-194 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.17 (1H, s, Ar**H**), 7.98 (2H, dd, *J* = 12.9, 7.6 Hz, Ar**H**), 7.47 (1H, t, *J* = 7.6 Hz, Ar**H**), 6.18 (2H, Bro, PhCON**H**$_2$), 1.35 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 169.4, 138.3, 132.9, 132.5, 130.7, 128.2, 84.2, 24.9; ESI-MA: Calculated for $C_{13}H_{18}BNNaO_3$ $[M+Na]^+$:270.1277. Found: 270.1299.

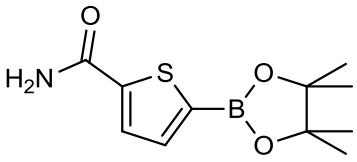
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (Entry 4, Table 4.10)



4.22

Following **general procedure III**, used 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) furan-2-carbaldehyde (0.44 g, 2 mmol) to give the title compound as a brown solid (0.36 g, 75.2%); m.p.: 148-150 °C; ^{1}H NMR (300 MHz, MeOD, 25 °C): δ 7.41 (1H, d, *J* = 2.6 Hz, furyl), 7.11 (1H, d, *J* = 2.6 Hz, furyl), 6.44 (2H, bro, **H**$_2$NCO), 1.19 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, MeOD, 25 °C): δ 160.6, 144.5, 115.3, 112.3, 82.9, 24.5; ESI-MA: Calculated for $C_{11}H_{17}BNO_4$ $[M+H]^+$:238.1251. Found: 238.1315; IR: v (cm-1) = 1674.92 (C=O stretch)

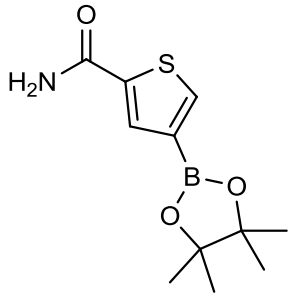
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (Entry 5, Table 4.10)



4.23

Following **general procedure III**, used 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) thiophene-2-carbaldehyde (0.47 g, 2 mmol) to give the title compound as a yellow solid (0.36 g, 70.7%); m.p.: 135-137 °C; ^{1}H NMR (300 MHz, MeOD, 25 °C): δ 7.73 (2H, dd, *J* = 11.6, 4.4 Hz, **H**$_2$NCO), 7.68 (1H, dd, *J* = 11.6, 4.4 Hz, thiophene), 7.14 (1H, dd, *J* = 5.0, 3.8 Hz, thiophene), 1.23 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, MeOD, 25 °C): δ 167.0, 140.3, 132.6, 130.9, 129.2, 76.2, 25.4; ESI-MA: Calculated for $C_{11}H_{17}BNO_3S$ $[M+H]^+$:254.1022. Found: 254.1080; IR: v (cm-1) = 1657.22 (C=O stretch)

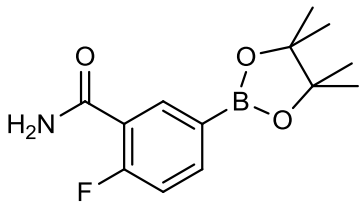
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-3-carboxamide (Entry 6, Table 4.10)



4.24

Following **general procedure III**, used 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) thiophene-3-carbaldehyde (0.47 g, 2 mmol) to give the title compound as a brown liquid (0.29 g, 57.6%), ^{1}H NMR (300 MHz, MeOD, 25 °C): δ 7.74-7.59 (3H, m, **H**$_2$NCO and thiophene), 7.09 (1H, s, furyl), 1.21 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, MeOD, 25 °C): δ 167.0, 139.6, 132.6, 131.0, 129.3, 84.5, 25.4; ESI-MA: Calculated for $C_{11}H_{17}BNO_3S$ $[M+H]^+$:254.1022. Found: 254.0995; IR: v (cm-1) = 1678.57 (C=O stretch)

2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Entry 7, Table 4.10)

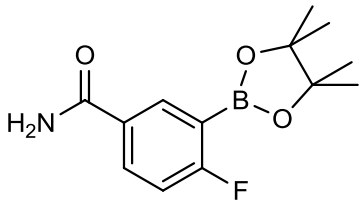


4.25

Following **general procedure III**, used 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (0.50 g, 2 mmol) to give the title compound as a colourless solid (0.34 g, 65.2%); m.p.: 132-135 °C; The product was observed as 2 rotamers in its NMR spectra. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.45 (1H, (major rotamer), dd, *J* = 8.5, 1.4 Hz, Ar**H**), 8.40-7.95 (1H, (minor rotamer), m, Ar**H**), 7.84 (1H, (major rotamer), dd, *J* = 10.6, 4.7 Hz, Ar**H**), 7.56-7.32 (1H, (minor rotamer), m, Ar**H**),

7.17 (1H, (major rotamer), t, *J* = 7.6 Hz, Ar**H**), 7.04 (4H, (minor and major rotamers), bro, **H**$_2$NCO), 6.73 (1H, (minor rotamer), d, *J* = 9.9 Hz, Ar**H**), 1.26 (12H, (major rotamer), s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$), 1.18 (12H, (minor rotamer), s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 163.2 (d, *J* = 291.5 Hz), 140.4, 139.3 (d, *J* = 2.2 Hz), 134.0 (d, *J* = 9.4 Hz), 132.3, 124.8 (d, *J* = 3.2 Hz), 115.7, 84.2, 24.8; ESI-MA: Calculated for $C_{13}H_{17}BFNNaO_3$ $[M+Na]^+$:288.1183. Found: 288.1206; IR: v (cm-1) = 1663.74 (C=O stretch)

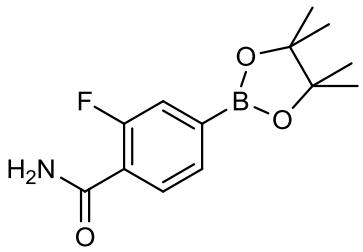
4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Entry 8, Table 4.10)



4.26

Following **general procedure III**, used 4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (0.50 g, 2 mmol) to give the title compound as a green solid (0.35 g, 66.4%); m.p.: 133-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.92 (1H, d, *J* = 3.2 Hz, Ar**H**), 7.78 (1H, dd, *J* = 8.7, 5.1 Hz, Ar**H**), 7.28 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.16 (2H, bro, **H**$_2$NCO), 1.22 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 171.4, 166.7 (d, *J* = 250.6 Hz), 136.6 (d, *J* = 9.5 Hz), 131.8 (d, *J* = 9.1 Hz), 119.4, 118.4 (d, *J* = 23.1 Hz), 116.7 (d, *J* = 22.1 Hz), 84.5, 25.4; ESI-MA: Calculated for $C_{13}H_{18}BFNO_3$ $[M+H]^+$:266.1364. Found: 266.1384; IR: v (cm-1) = 1668.42 (C=O stretch)

2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Entry 9, Table 4.10)



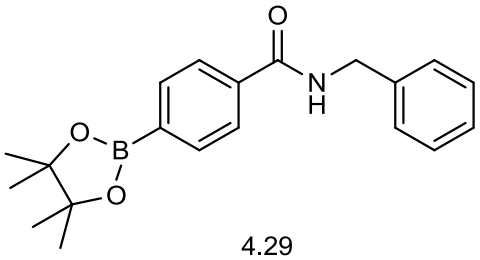
4.27

Following **general procedure III**, used 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (0.50 g, 2 mmol) to give the title compound as a colourless solid (0.38 g, 72.3%); m.p.: 140-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.49 (1H, s, Ar**H**), 7.36 (1H, dd, *J* = 13.6, 8.1 Hz, Ar**H**), 7.20-7.12 (1H, m, Ar**H**), 6.24 (2H, Bro, $\mathbf{H}_2NCO$), 1.19 (12H, s, $(C\mathbf{H}_3)_2CC(C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 168.4, 162.7 (d, *J* = 247.8 Hz), 130.3 (d, *J* = 7.9 Hz), 122.9 (d, *J* = 3.1 Hz), 119.1 (d, *J* = 21.3 Hz), 114.8 (d, *J* = 23.0 Hz), 83.1, 24.5; ESI-MA: Calculated for $C_{13}H_{18}BFNO_3$ $[M+H]^+$:266.1364. Found: 266.1353; IR: v (cm-1) = 1671.69 (C=O stretch)

6.5.4 General Procedure IV for the Preparation of Secondary boronic amide

The primary amide species (1 mmol) was added to an oven dried Radleys carousel tube, followed by toluene (2 mL) and benzylamine (1.2 mmol). Hydroxylamine hydrochloride (64.6 mg, 100 mol %) was then added and the carousel tube was sealed before the reaction mixture was heated at reflux. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and 20 mL dichloromethane added. The reaction mixture was then washed with water (2 x 30 mL) to remove the hydroxylamine hydrochloride, and the resulting organic layer was dried over MgSO4. The solution was concentrated *in vacuo* and then analysed by their ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data. All compounds were purify by column chromatography with DCM:MeOH (99:1).

N-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Entry 1, Table 4.11)

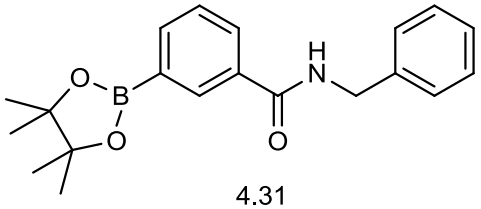


4.29

Following **general procedure IV**, used 4-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl) benzamide (0.24 g, 1 mmol) and benzylamine (0.13 ml, 1.2 mmol) to give the title compound as a colourless solid (0.32 g, 94.3%); m.p.: 76-78 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.99 (1H, d, *J* = 7.0 Hz, **H**NCH_2Ph), 7.73 (4H, dd, *J* = 23.5, 8.2 Hz, Ar**H**), 7.25-7.17 (5H, m, Ar**H**), 4.54 (2H, d, *J* = 7.0 Hz, HNC**H**$_2$Ph), 1.25 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 167.5, 138.1, 136.5, 135.1, 134.7, 131.9, 128.8, 127.9, 126.1, 84.1, 44.2, 24.9; ESI-MA: Calculated for $C_{20}H_{25}BNO_3$

$[M+H]^+$: 338.1927. Found: 338.1952; IR: v (cm-1) = 1658.33 (C=O stretch)

N-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Entry 2, Table 4.11)



4.31

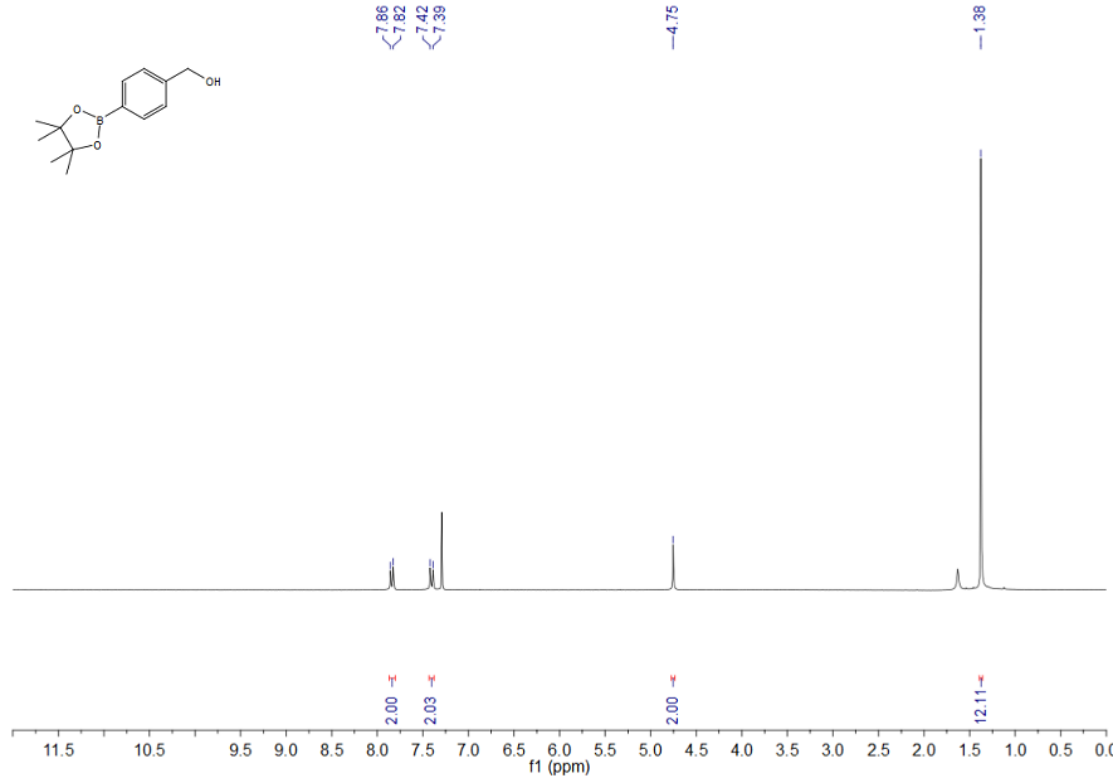
Following **general procedure IV**, used 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzamide (0.24 g, 1 mmol) and benzylamine (0.13 ml, 1.2 mmol) to give the title compound as a colourless solid (0.30 g, 90.2%); m.p.: 85-87 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.08 (1H, d, *J* = 7.0 Hz, **H**NCH_2Ph), 8.03 (1H, s, Ar**H**), 7.94 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.85 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.38 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.26-7.18 (5H, m, Ar**H**), 4.58 (2H, d, *J* = 7.0 Hz, HNC**H**$_2$Ph), 1.26 (12H, s, (C**H**$_3$)$_2$CC(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ 167.3, 138.7, 139.2, 137.9, 136.5, 133.6, 132.8, 132.2, 130.7, 128.7, 128.0, 84.2, 44.1, 24.8; ESI-MA: Calculated for $C_{20}H_{25}BNO_3$ $[M+H]^+$: 338.1927. Found: 338.1948; IR: v (cm-1) = 1669.11 (C=O stretch)

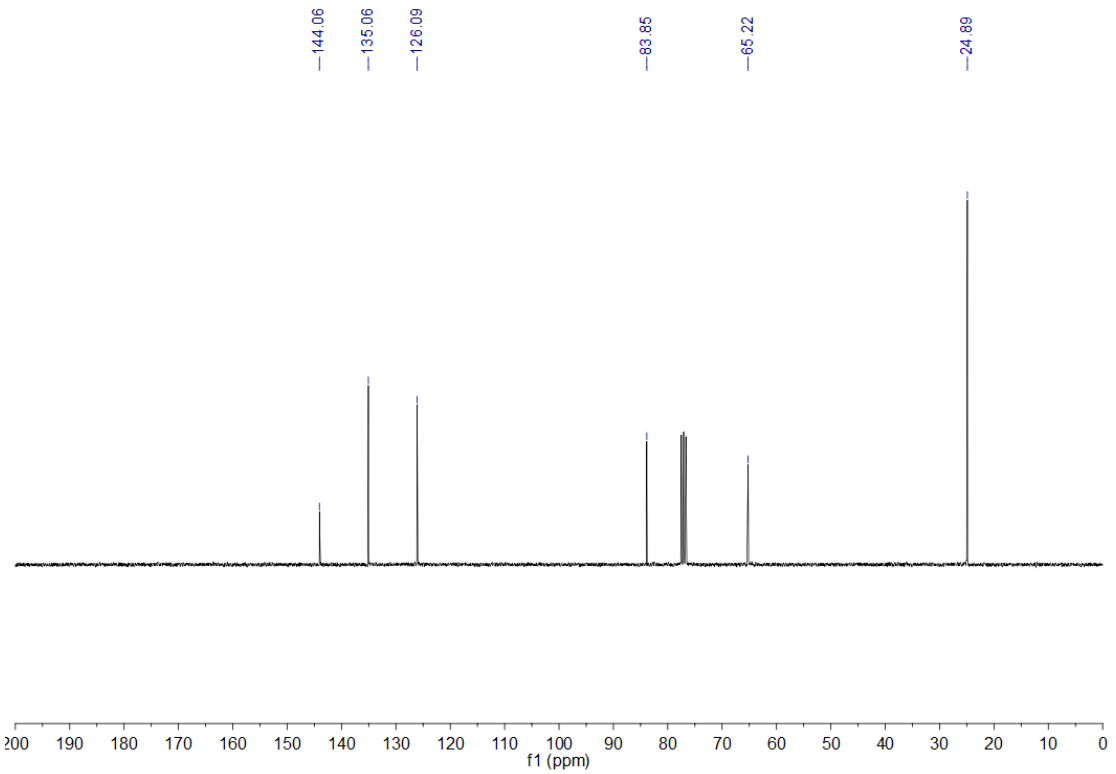
"In ^{13}C analysis, carbons next to the ^{11}B atom tend to be broadened or missing – often beyond detection limits."[108]

"19F is a spin 1/2 nucleus, so the n+1 rule applies to the splitting pattern. 1 fluorine nucleus will split the 13C signal into a doublet. So the carbond directly bound to the fluorine will appear as a dounblet with a large coupling constant (around 250 Hz). It might also get progressively smaller couplings for the meta and para carbon."[116]

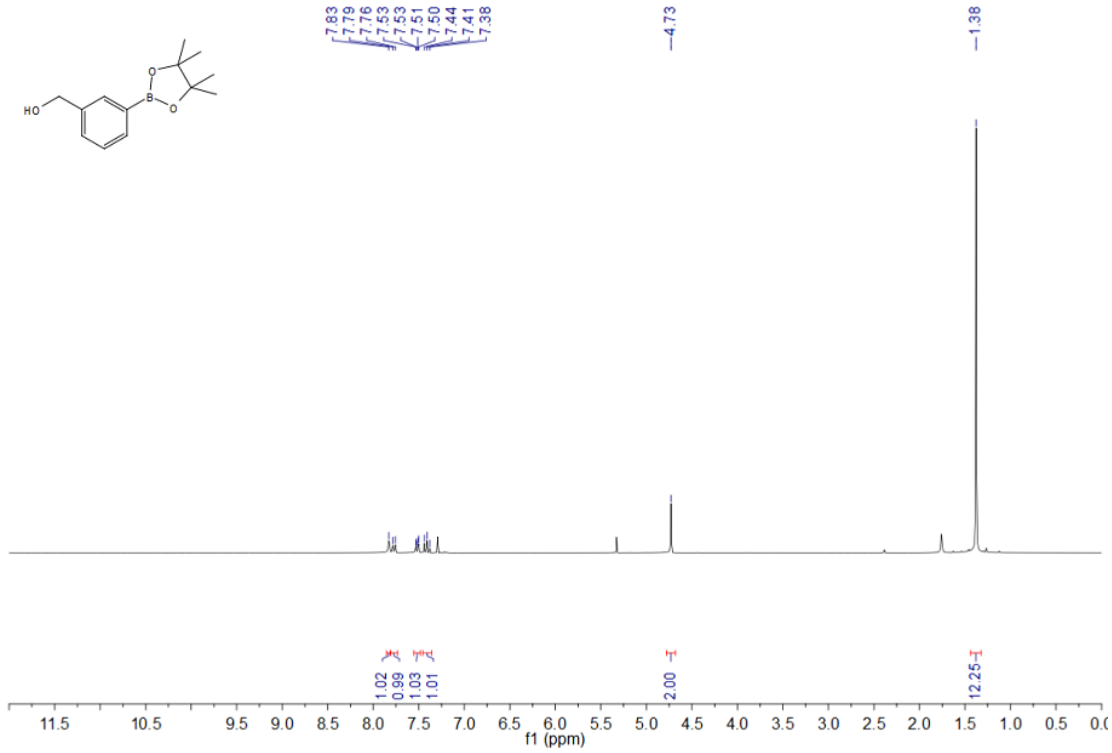
6 Appendix

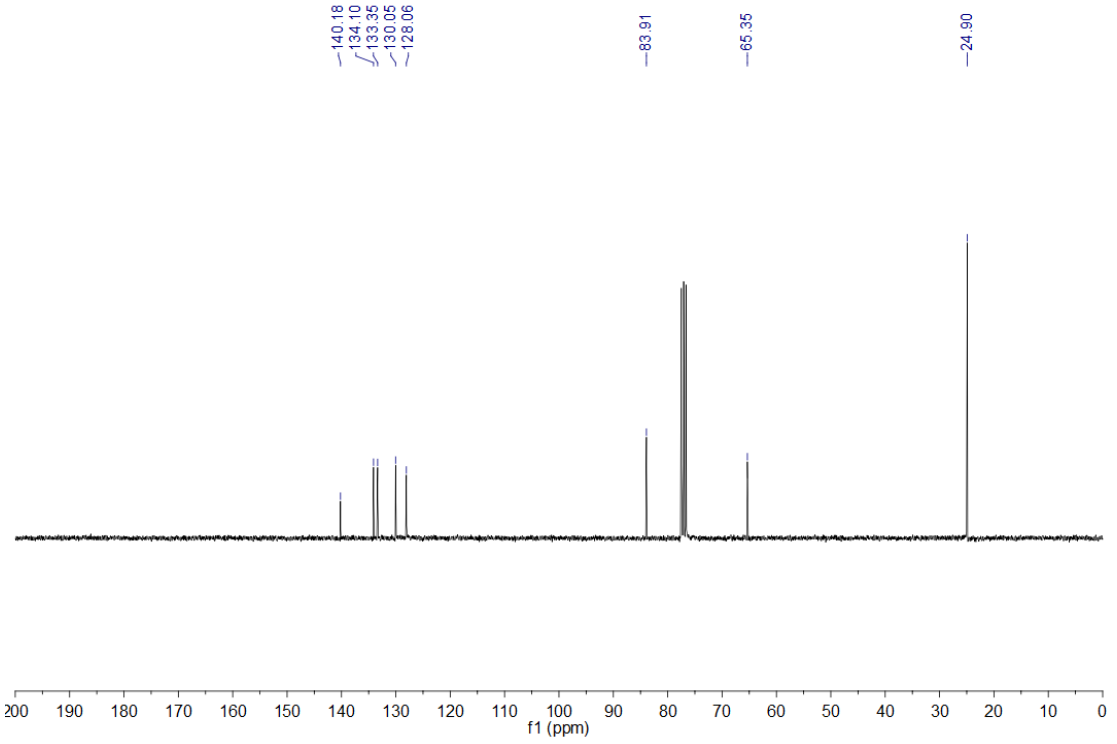
Compound 2.6



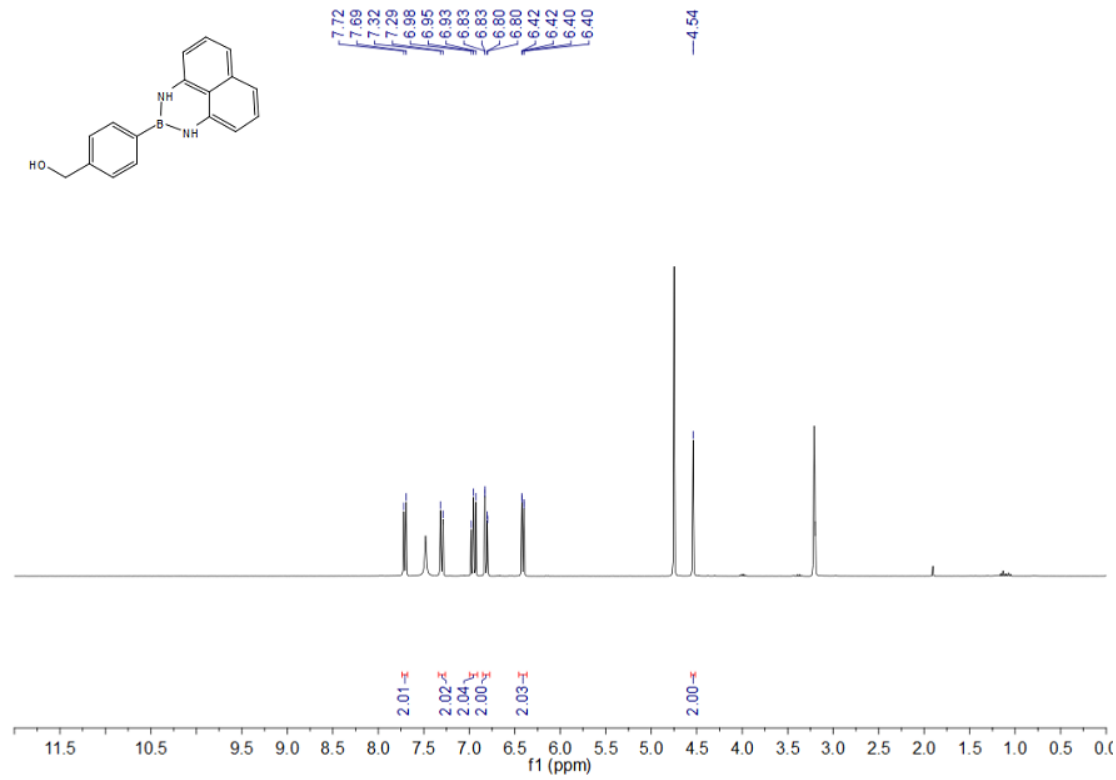


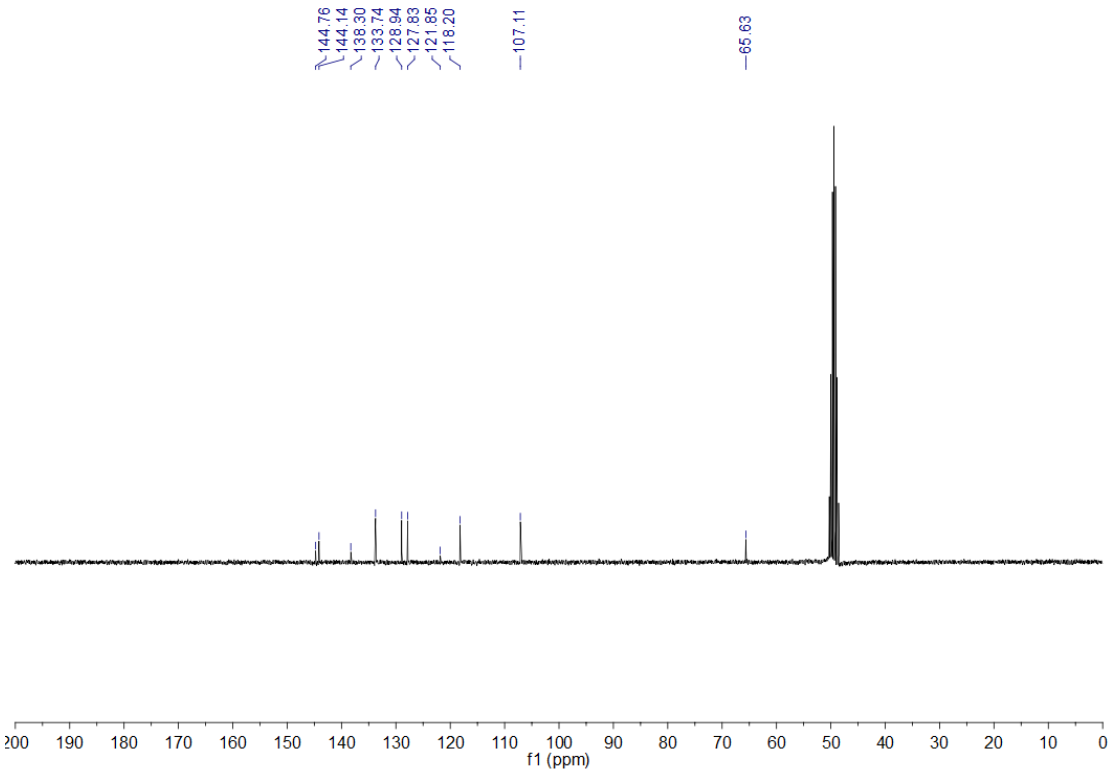
Compound 2.7


7.83
7.79
7.76
7.53
7.53
7.51
7.50
7.44
7.41
7.38
4.73
1.38
HO
B
O
O
1.02
0.99
1.03
1.01
2.00
12.25
f1 (ppm)

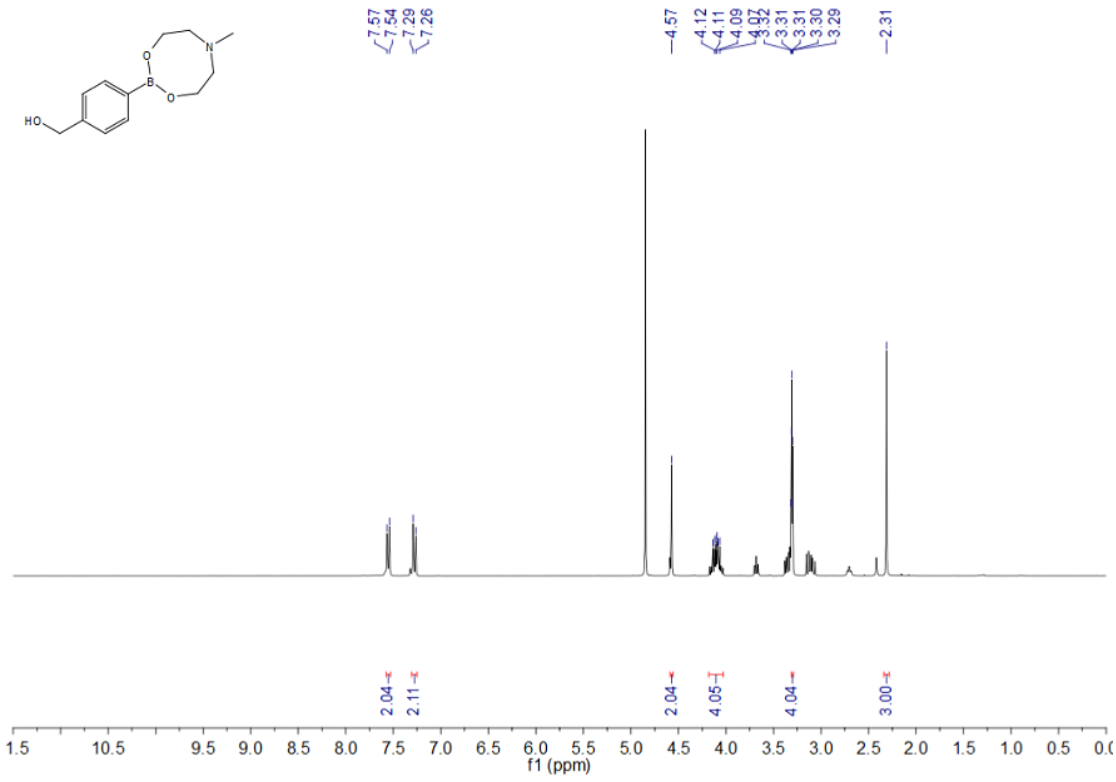

140.18
134.10
133.35
130.05
128.06
83.91
65.35
24.90
f1 (ppm)

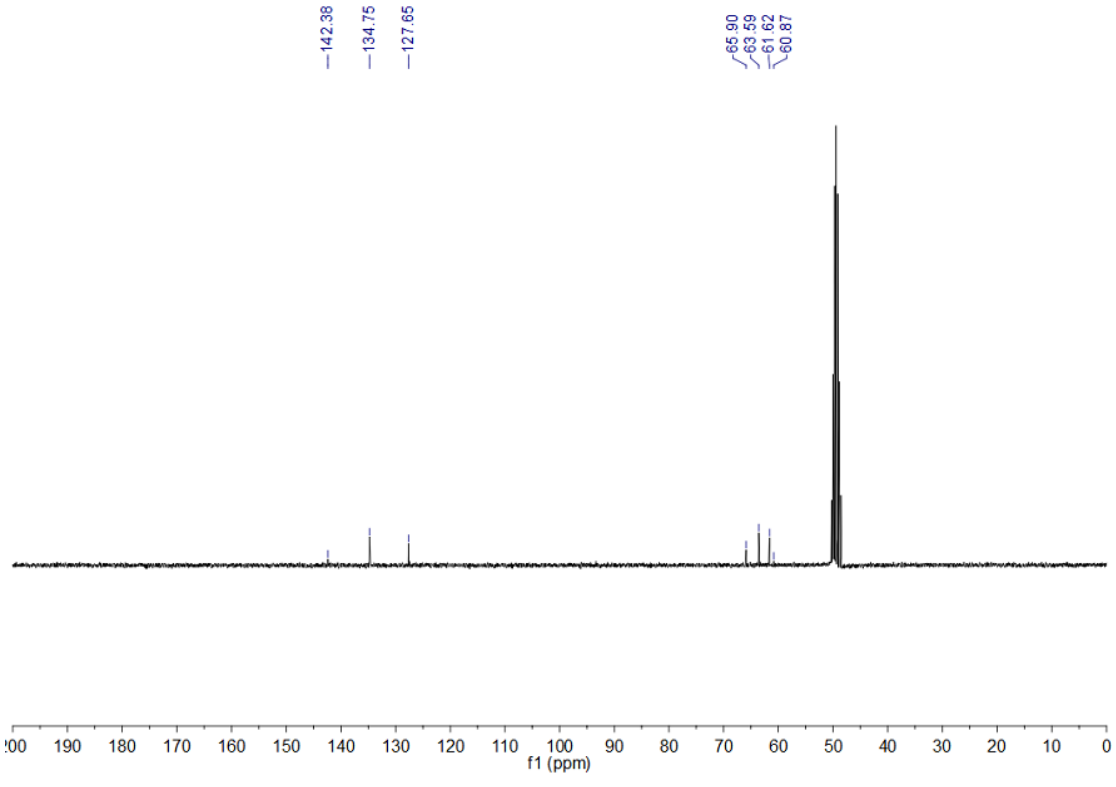
Compound 2.13



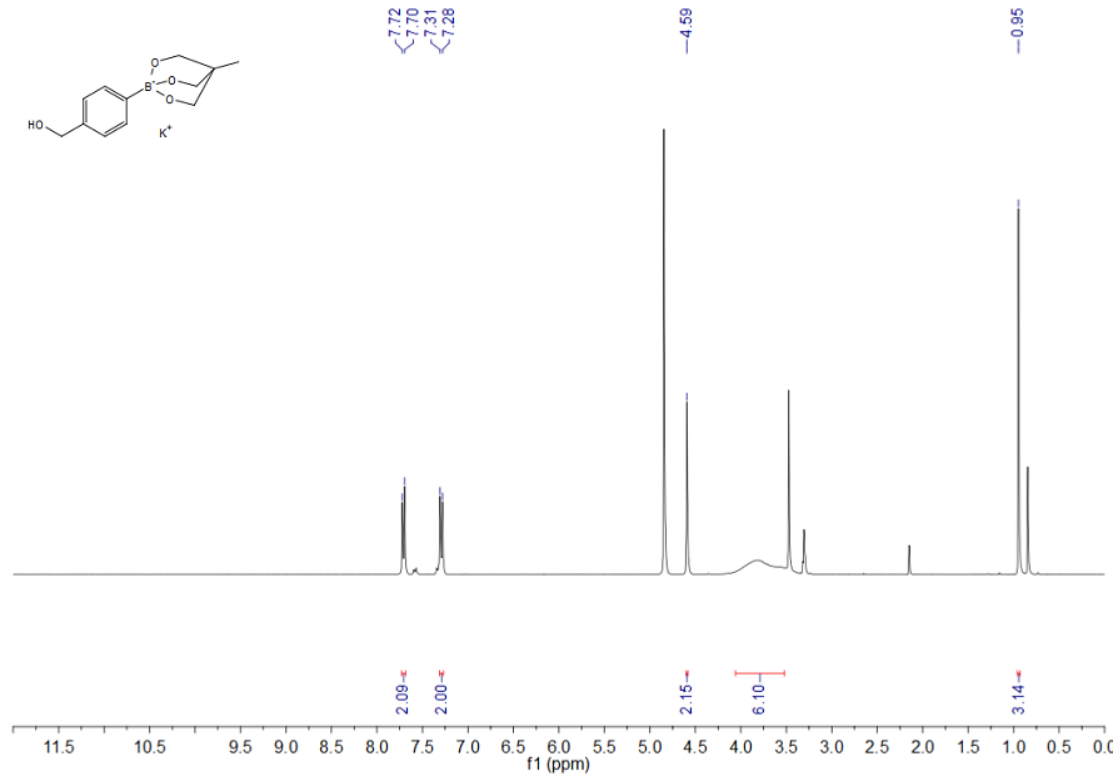


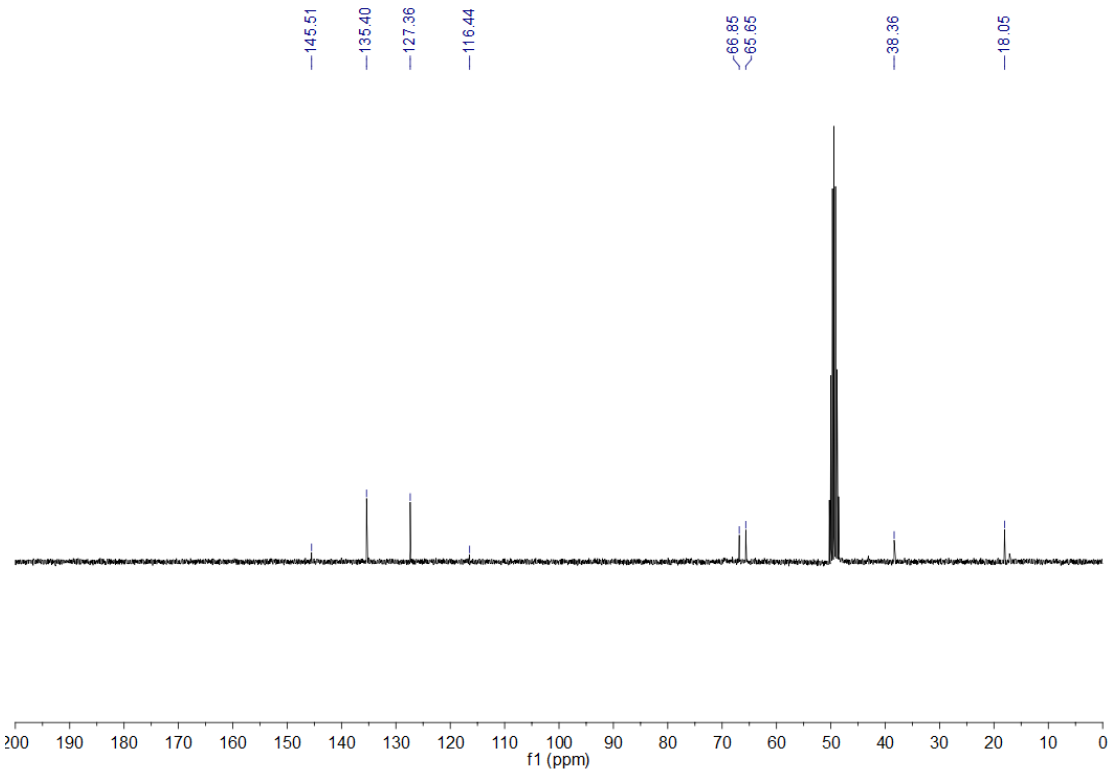
Compound 2.16



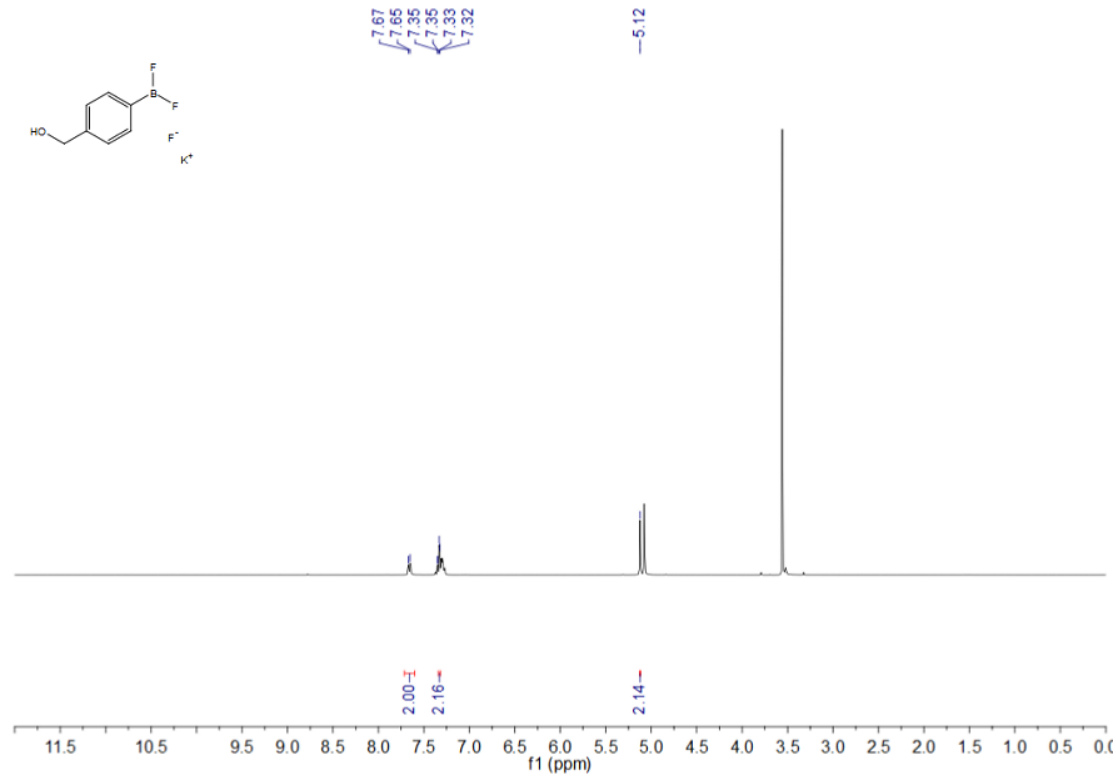


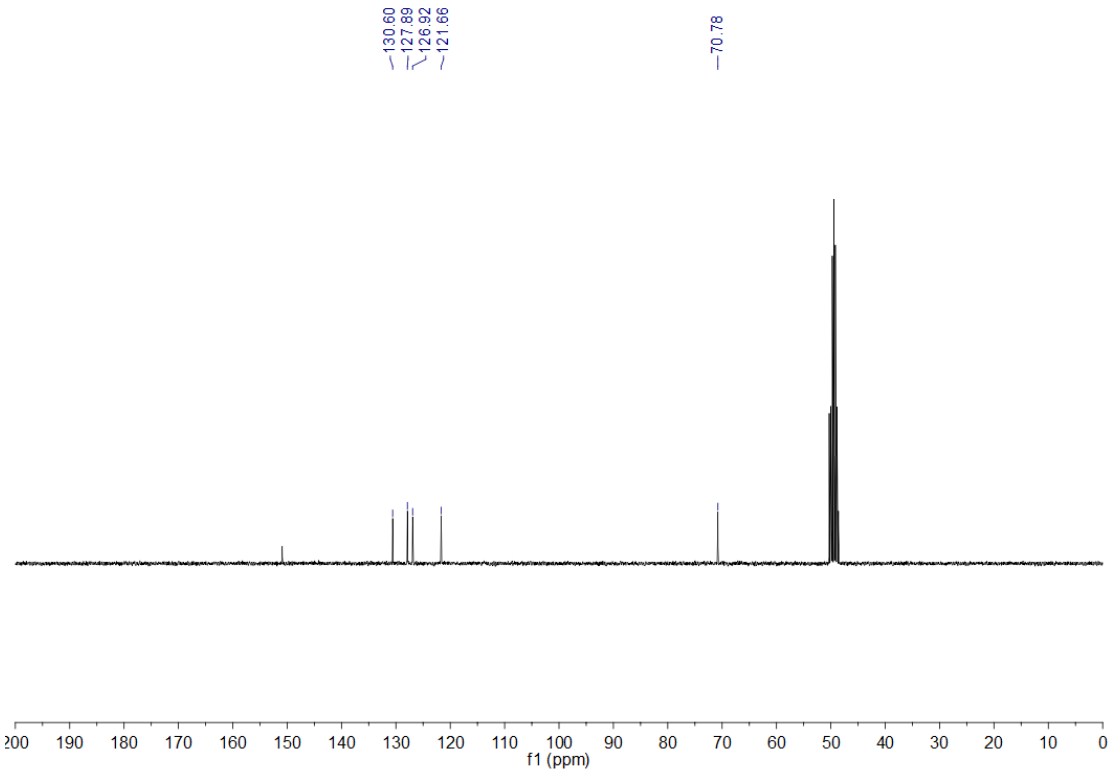
Compound 2.20



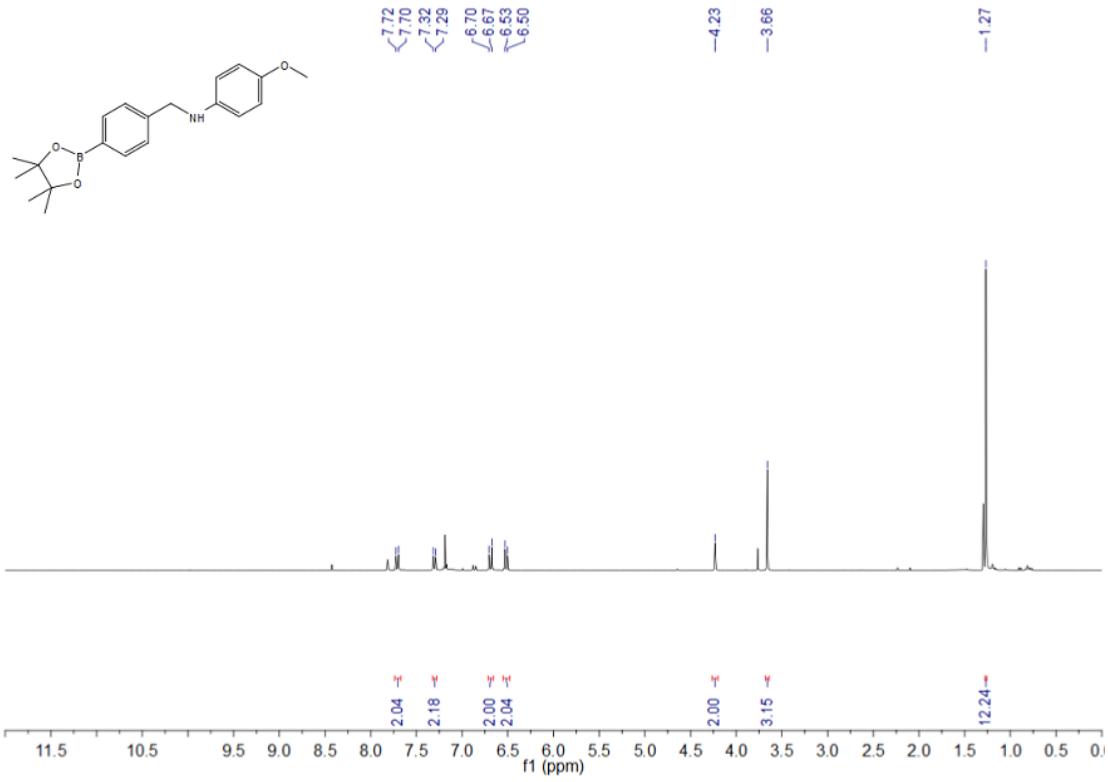


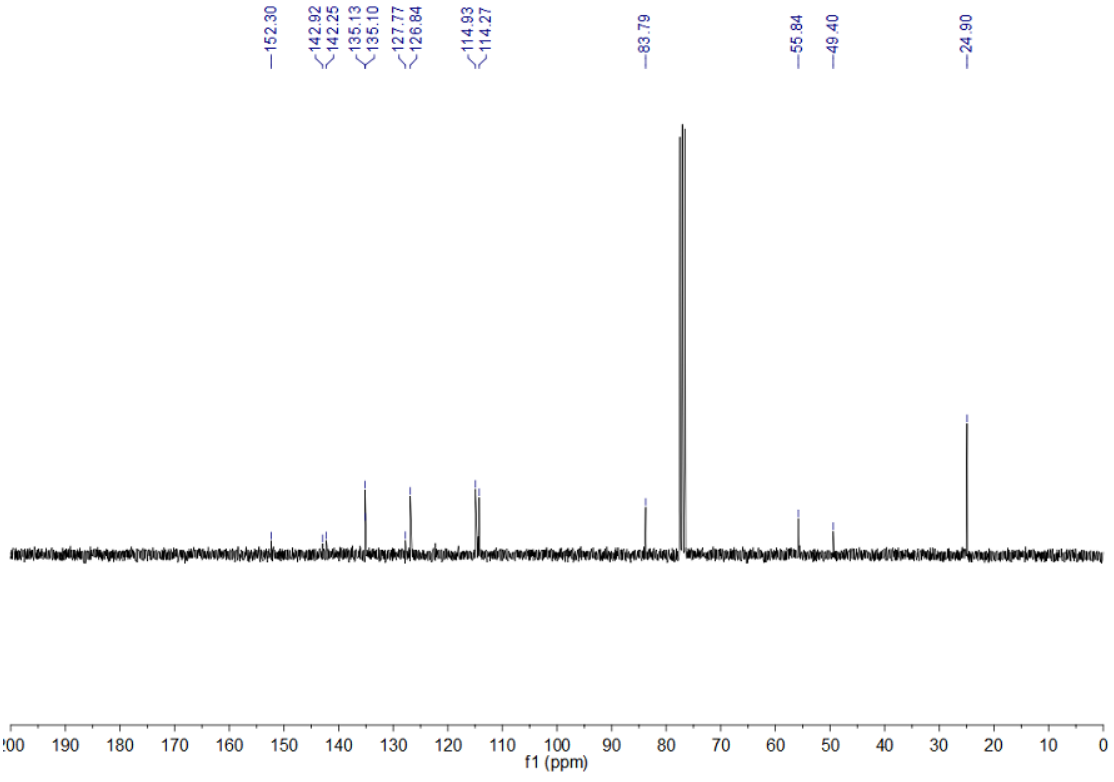
Compound 2.22



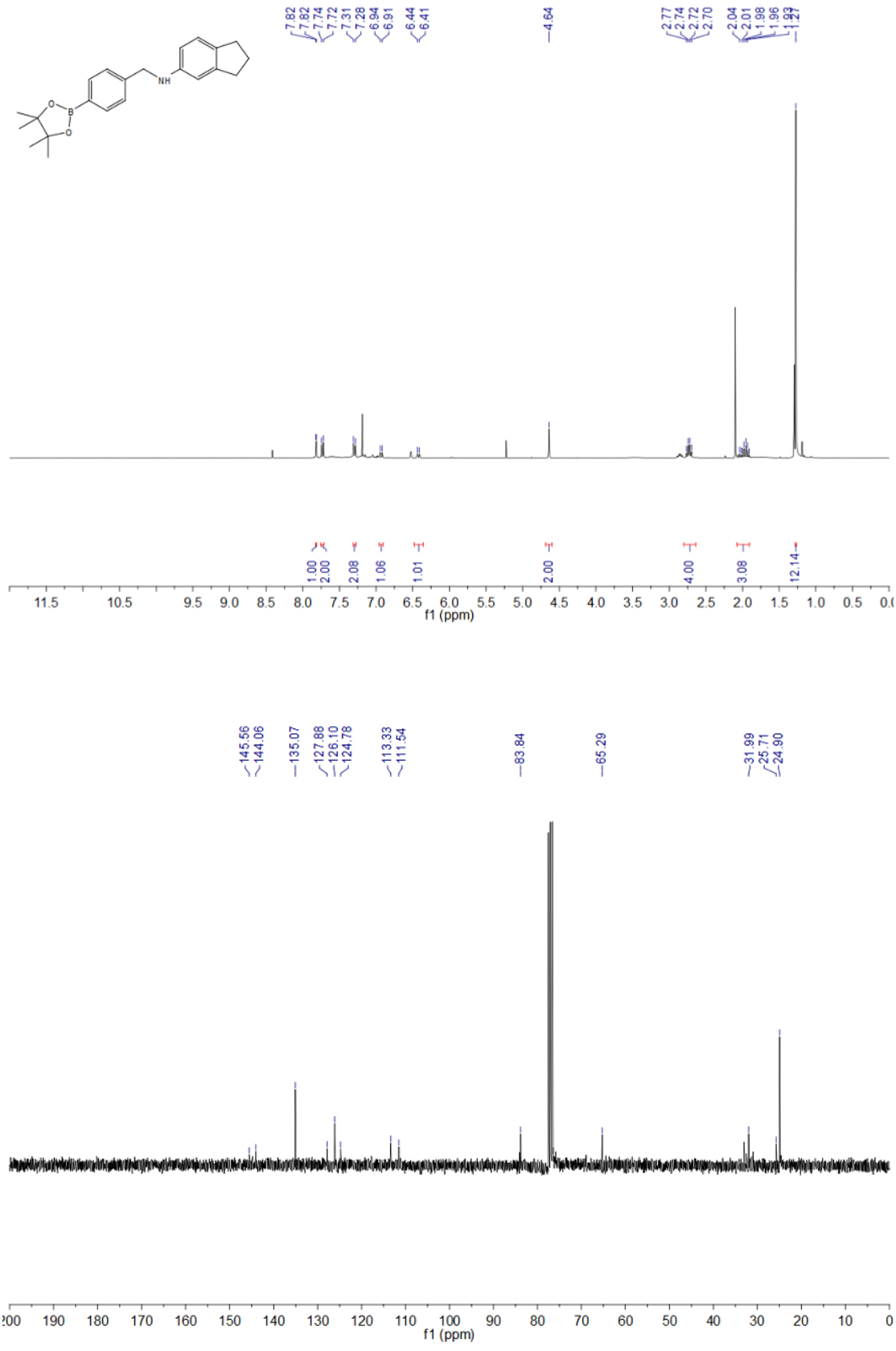


Entry 1 Table 2.17 Compound 2.36

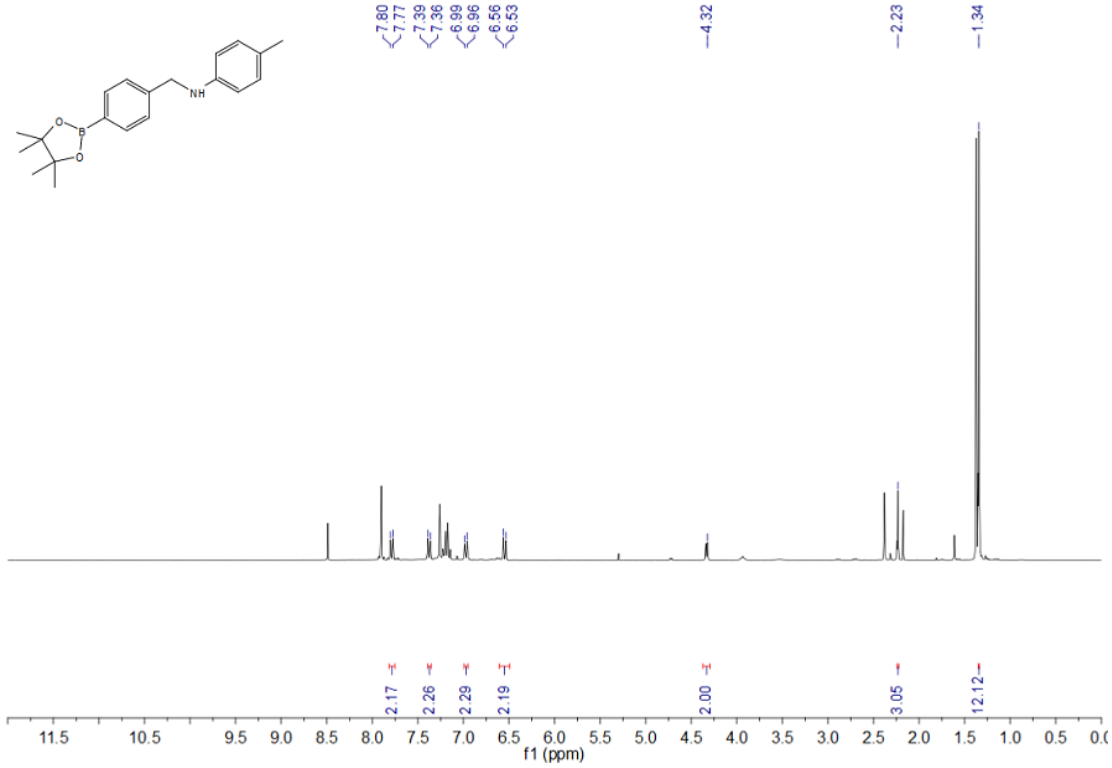


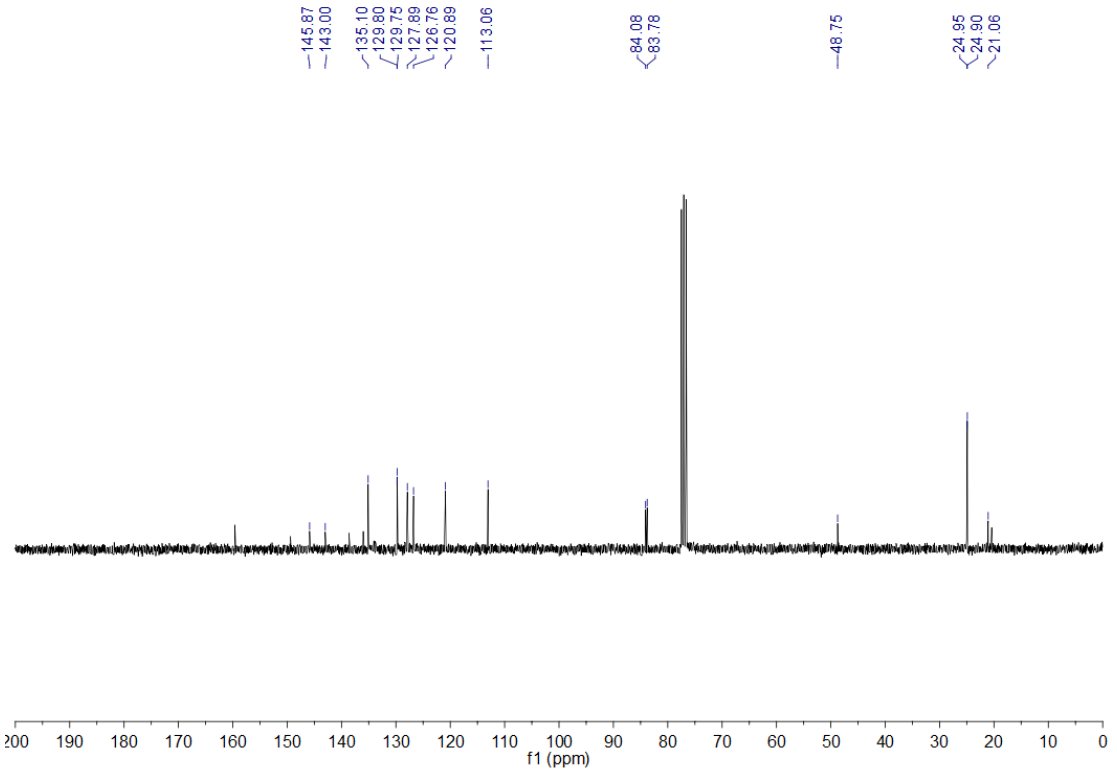


Entry 2 Table 2.17 Compound 2.37

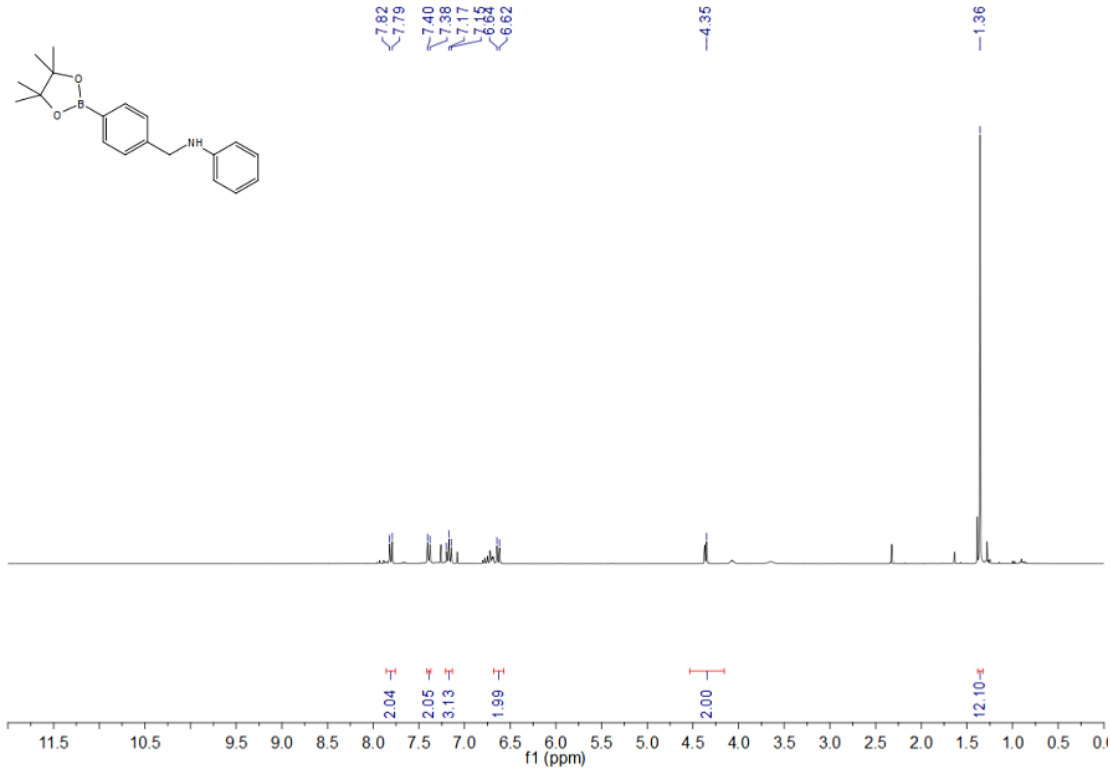


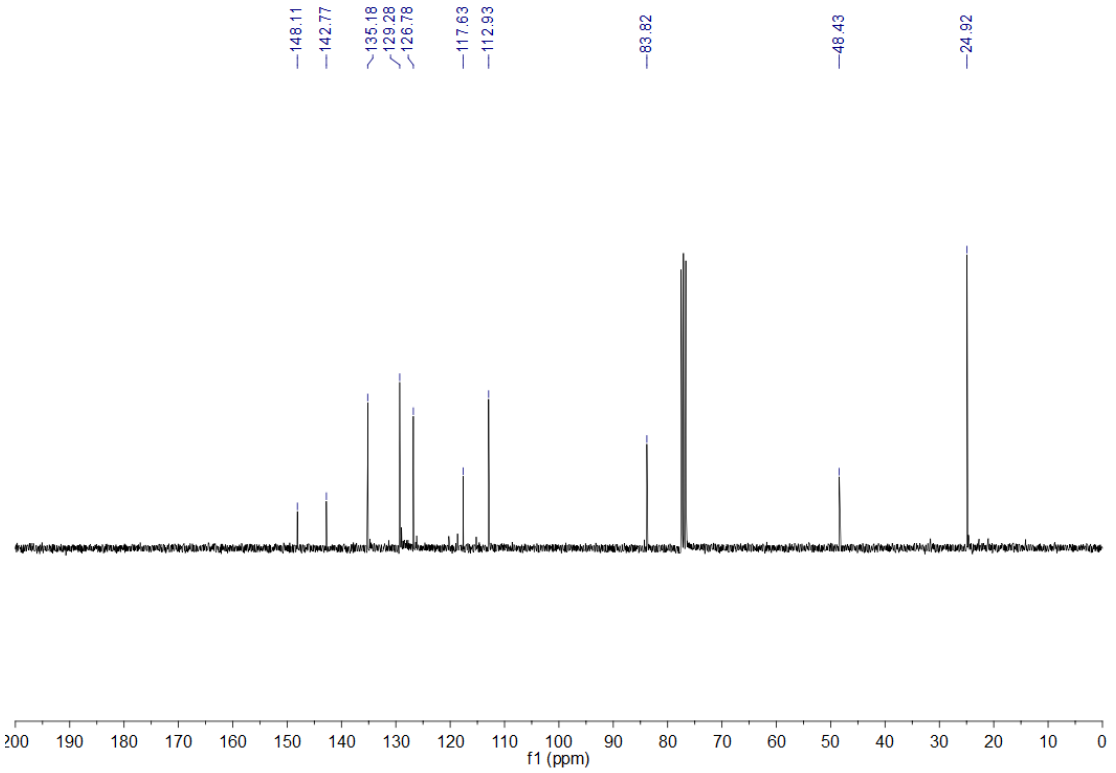
Entry 3 Table 2.17 Compound 2.38



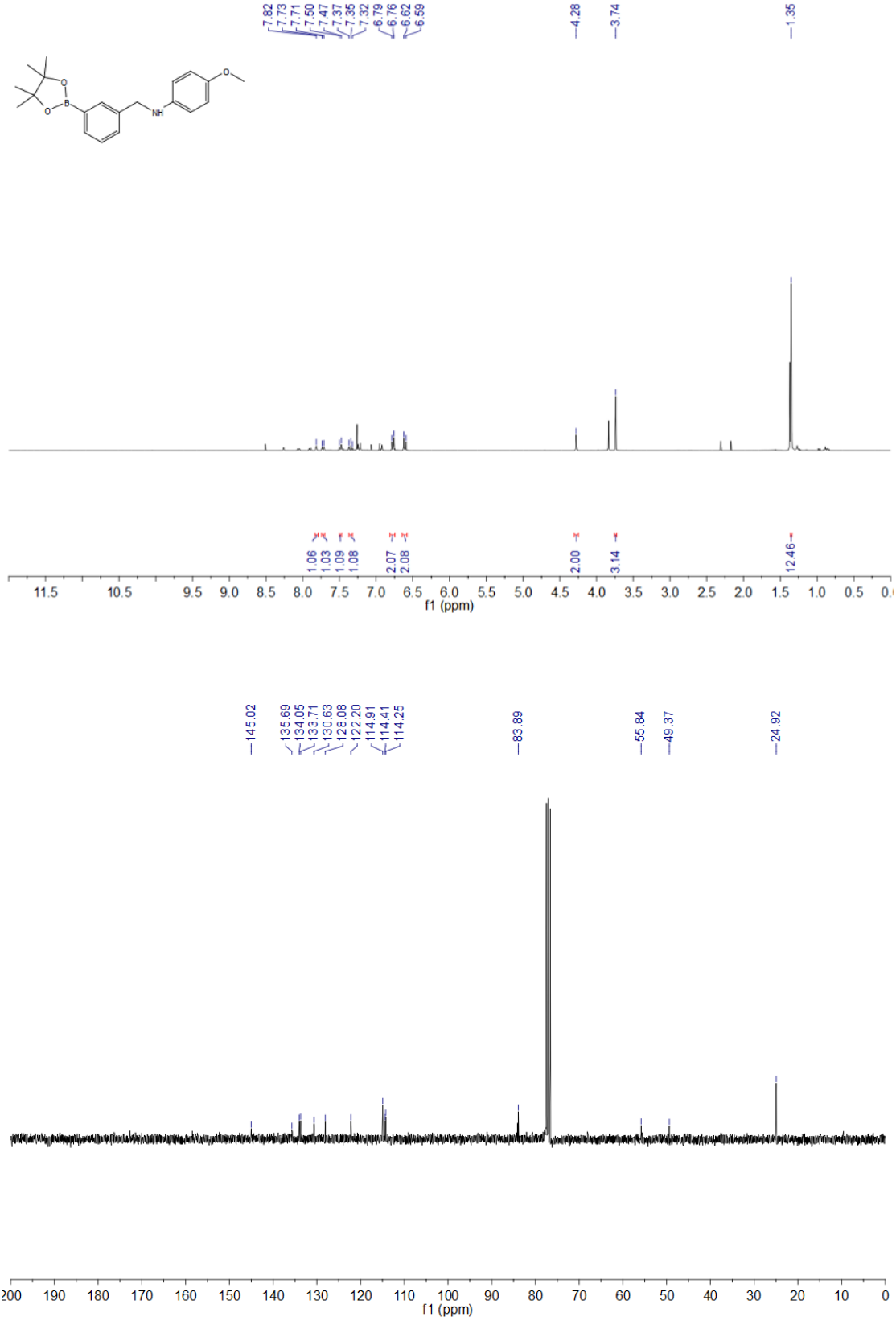


Entry 4 Table 2.17 Compound 2.39

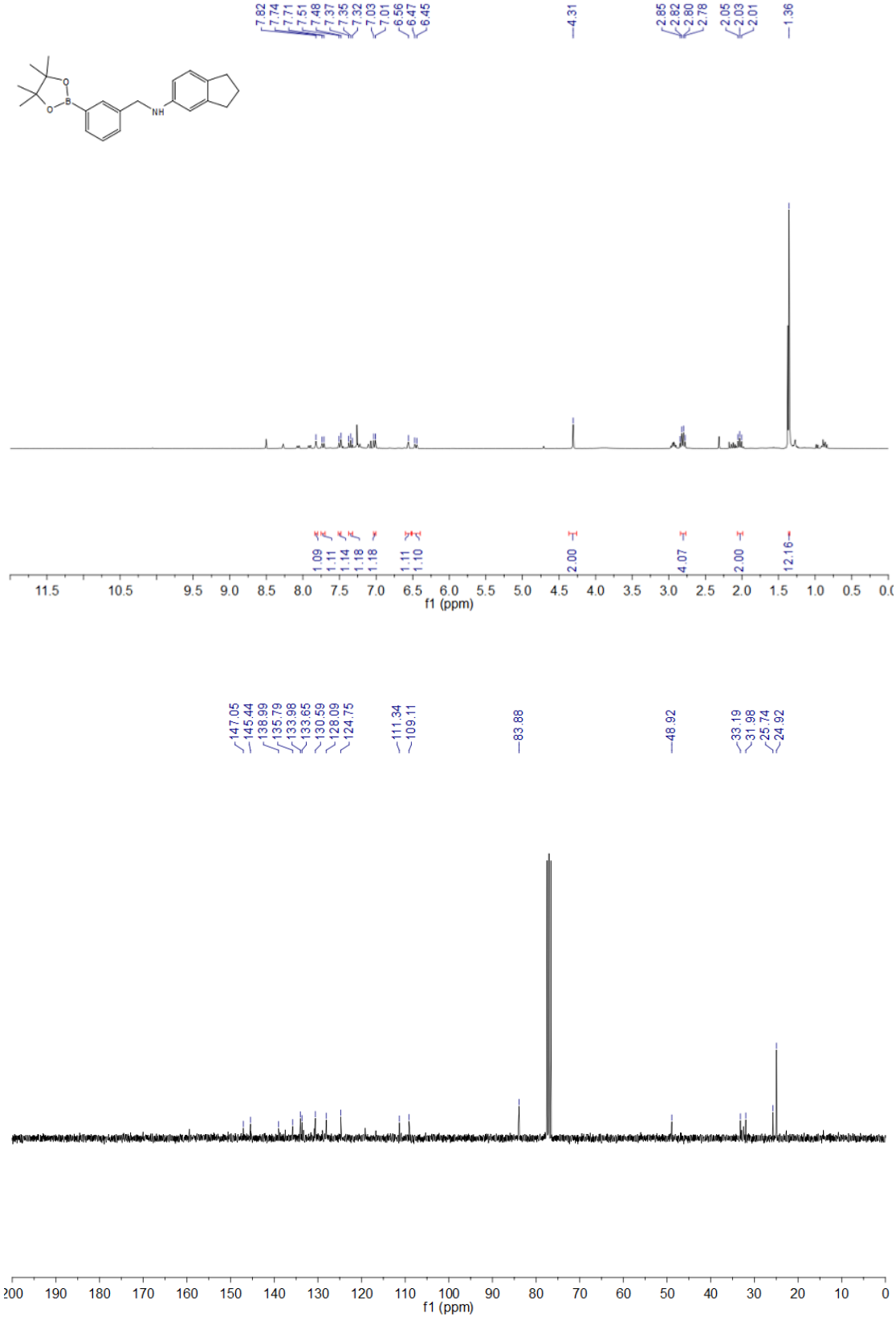




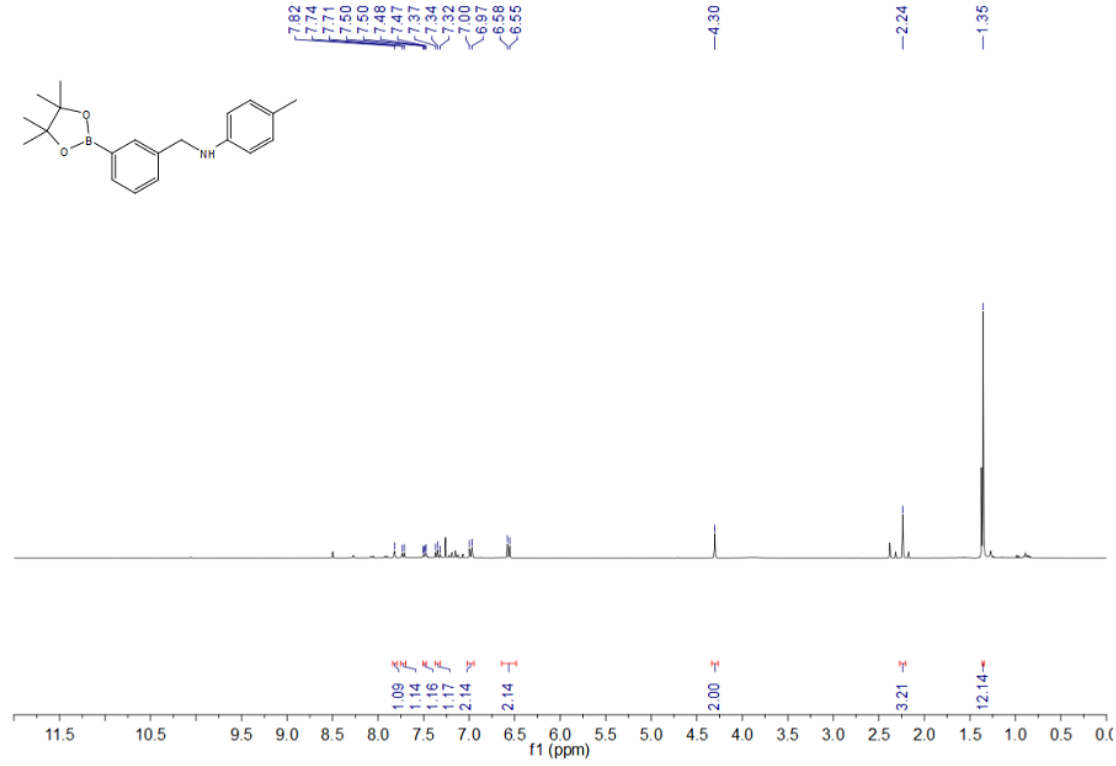
Entry 1 Table 2.18 Compound 2.41

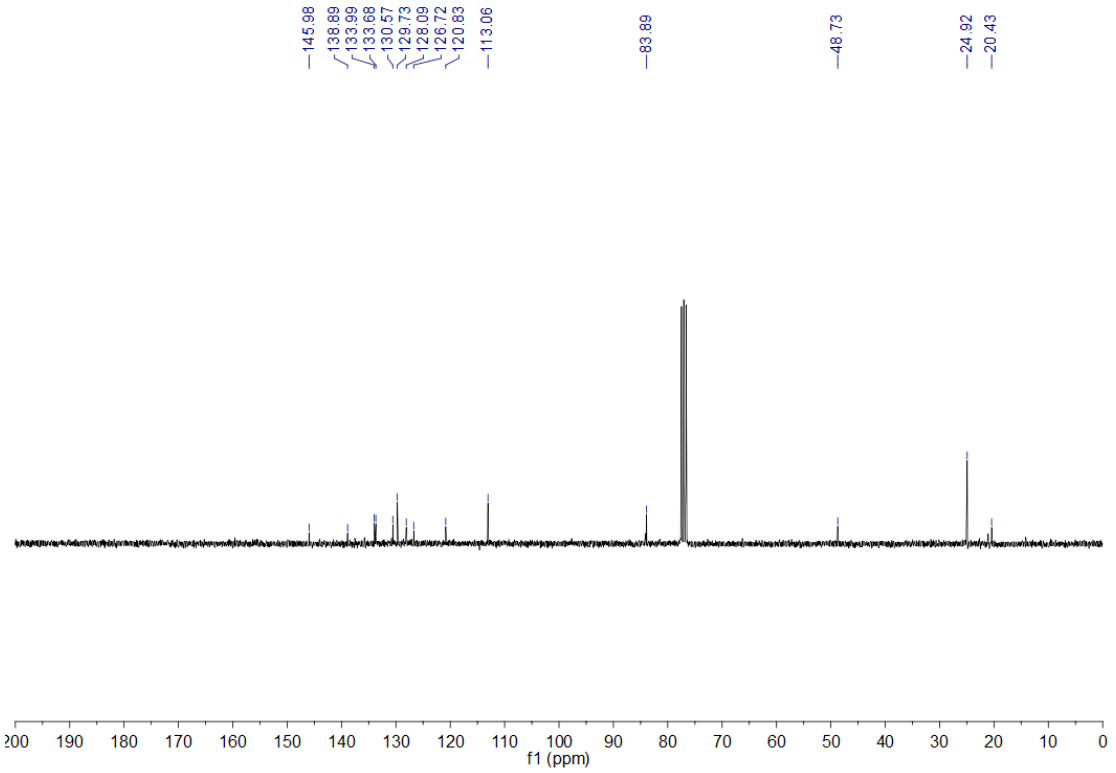


Entry 2 Table 2.18 Compound 2.42

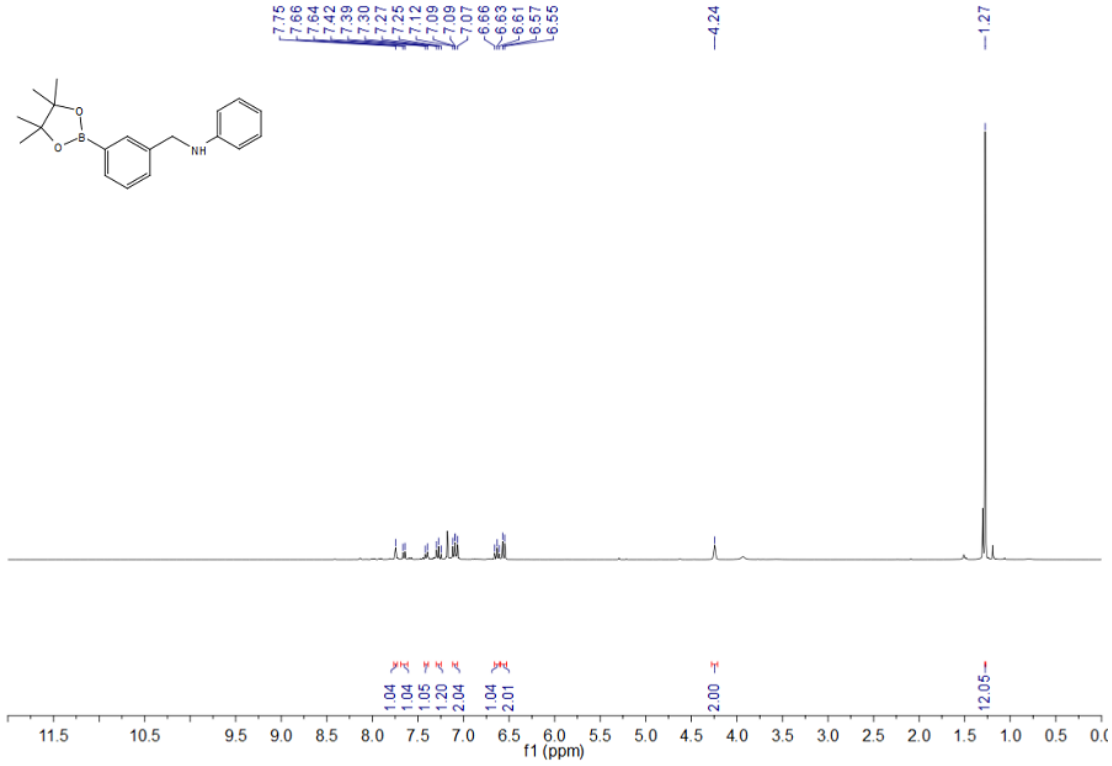


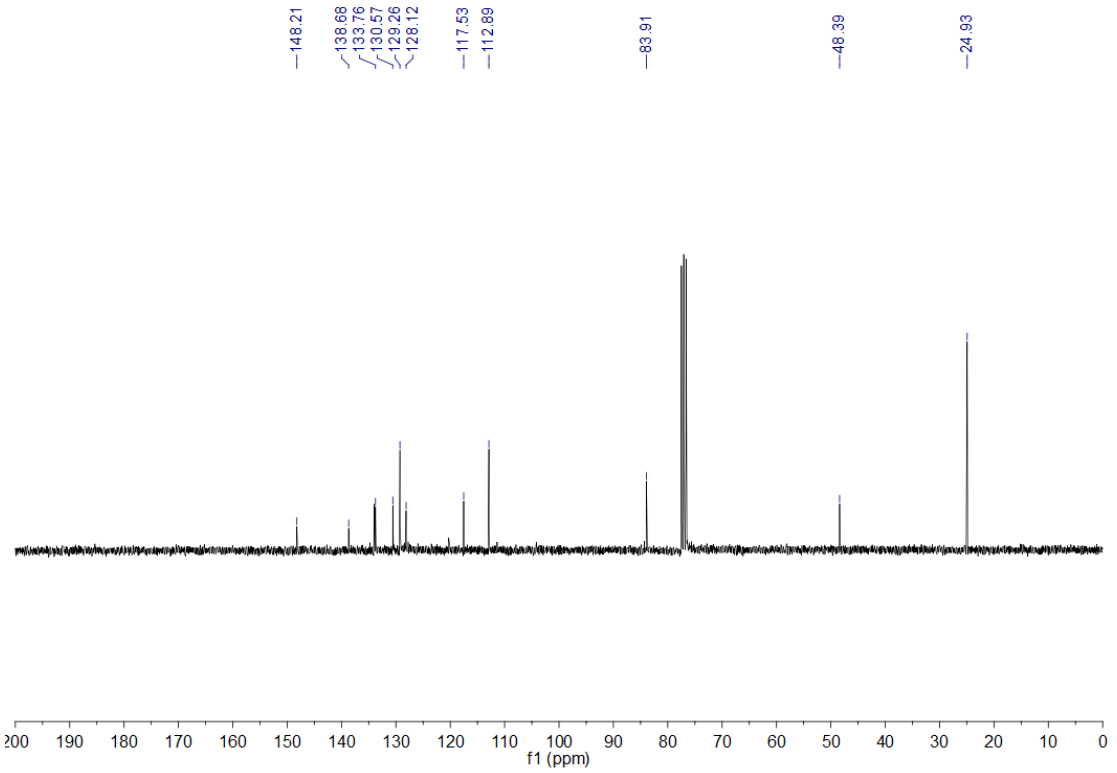
Entry 3 Table 2.18 Compound 2.43



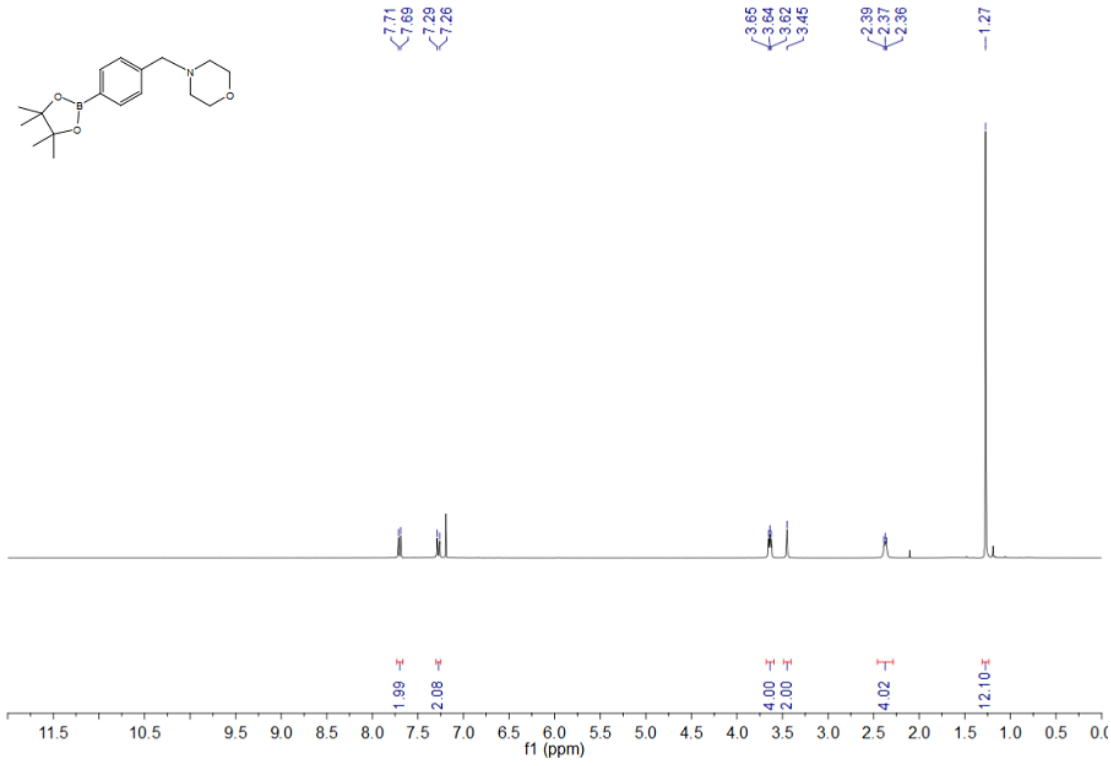


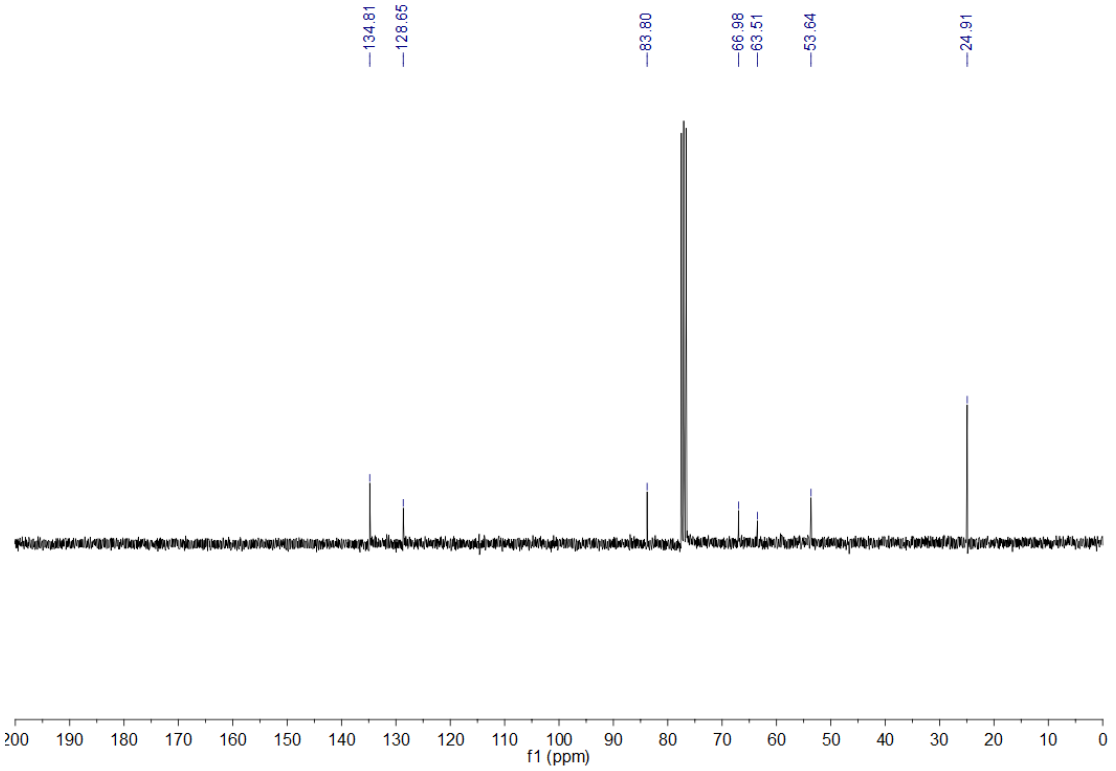
Entry 4 Table 2.18 Compound 2.44



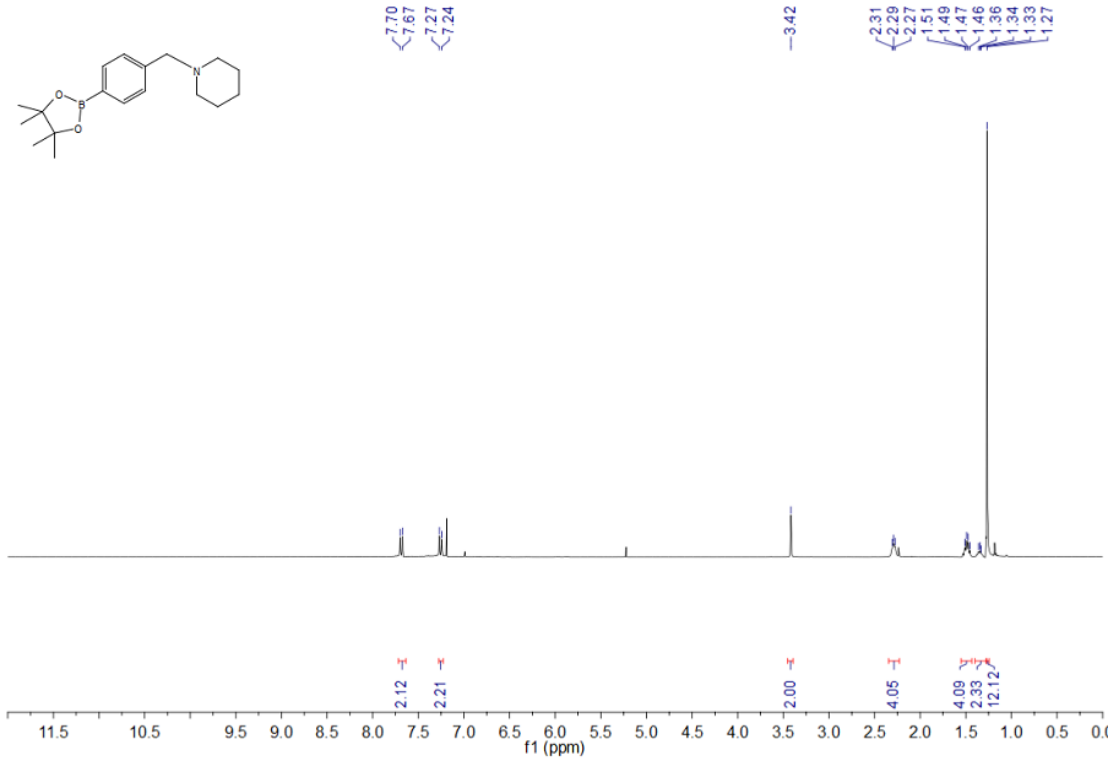


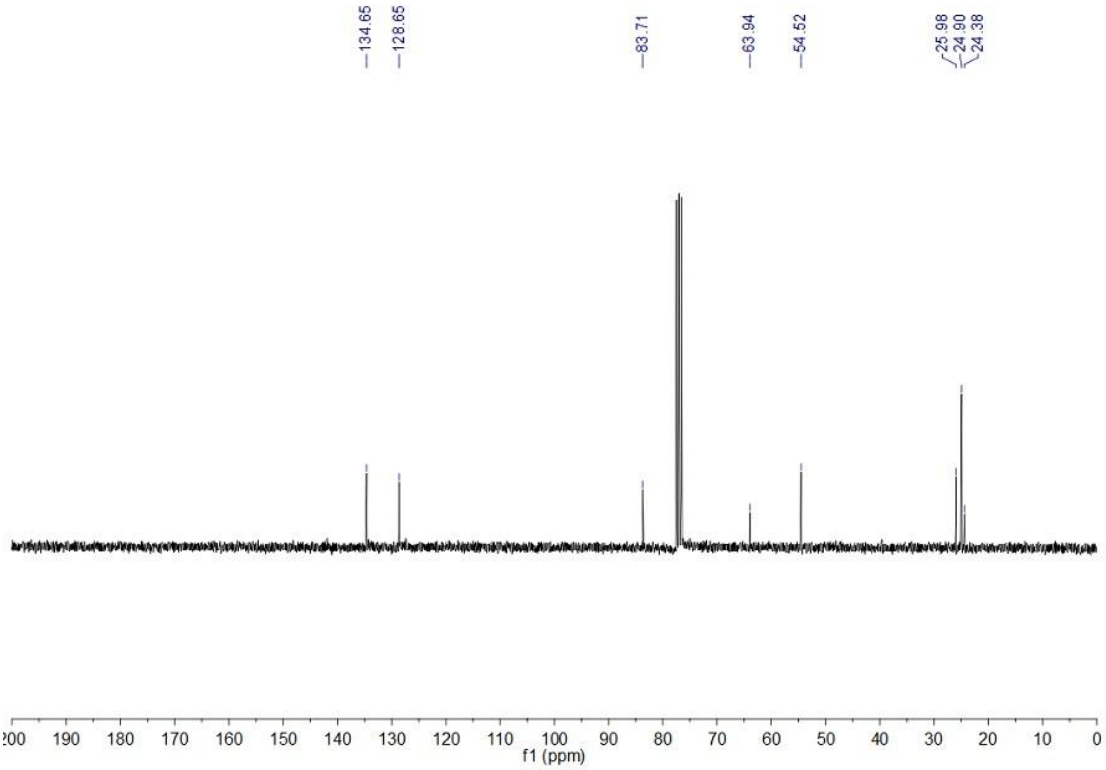
Entry 1 Table 2.19 Compound 2.8



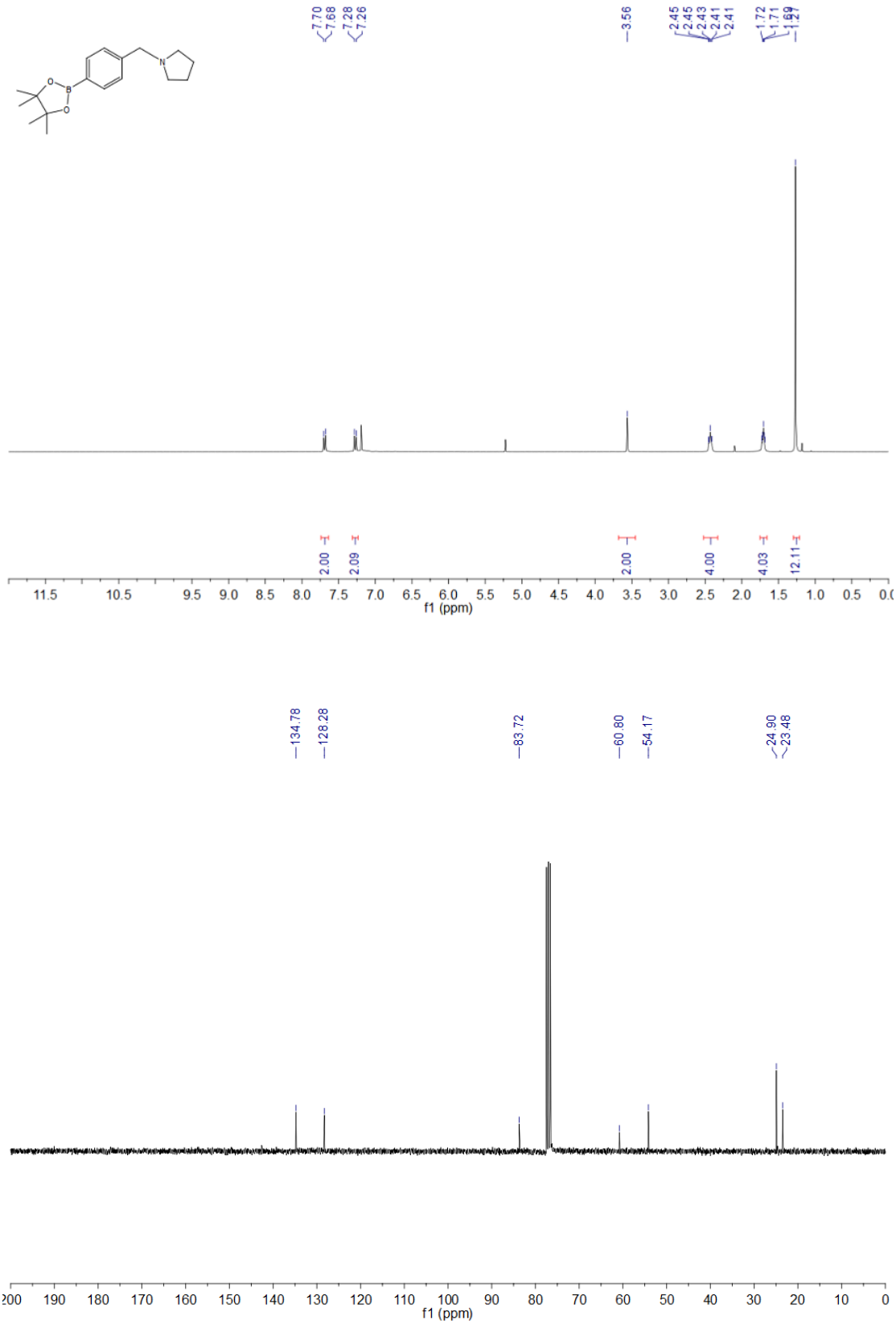


Entry 2 Table 2.19 Compound 2.24

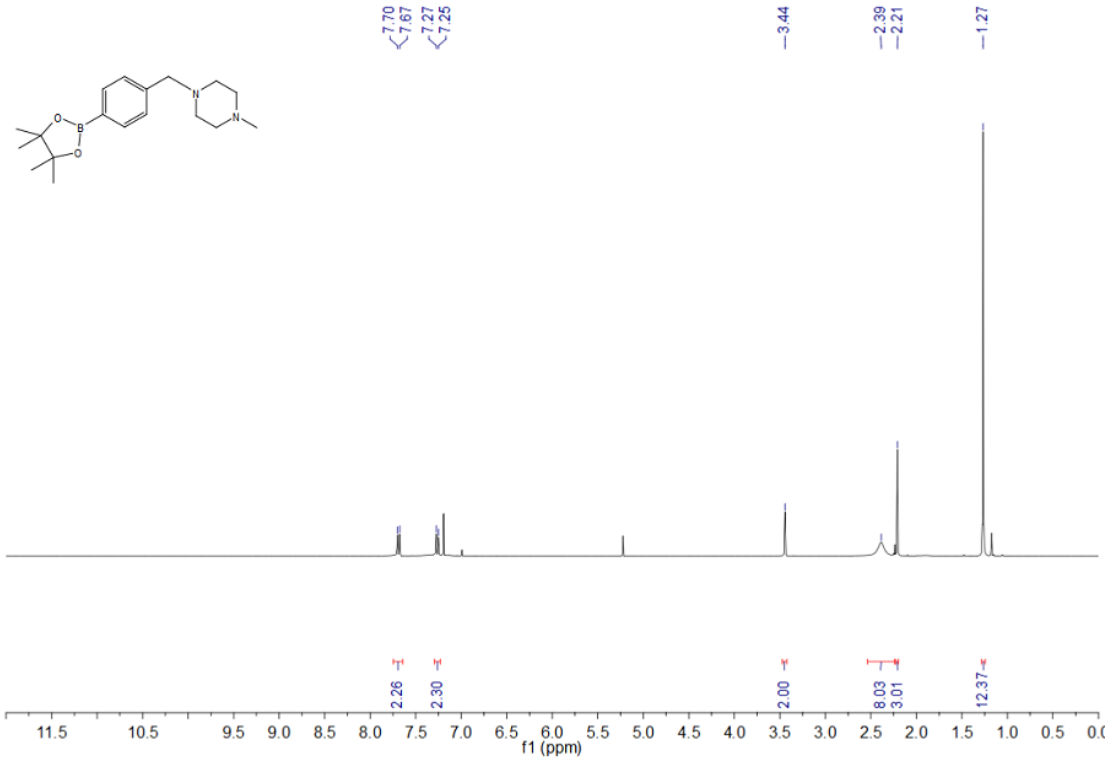


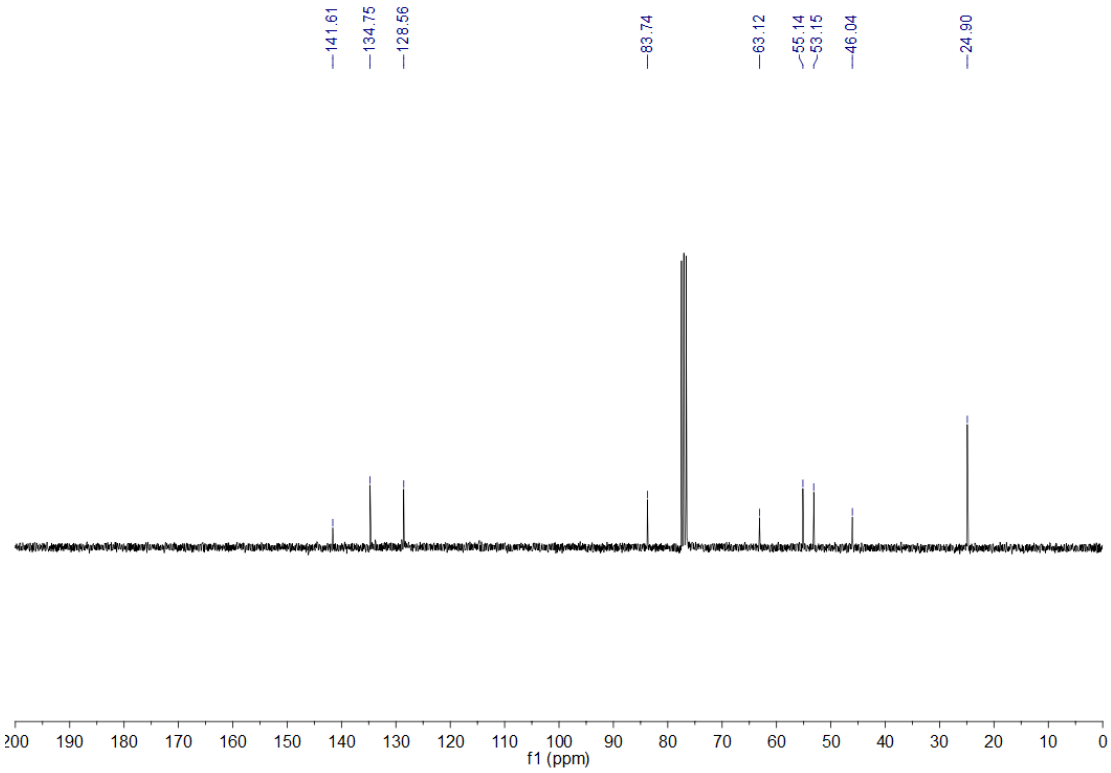


Entry 3 Table 2.19 Compound 2.25

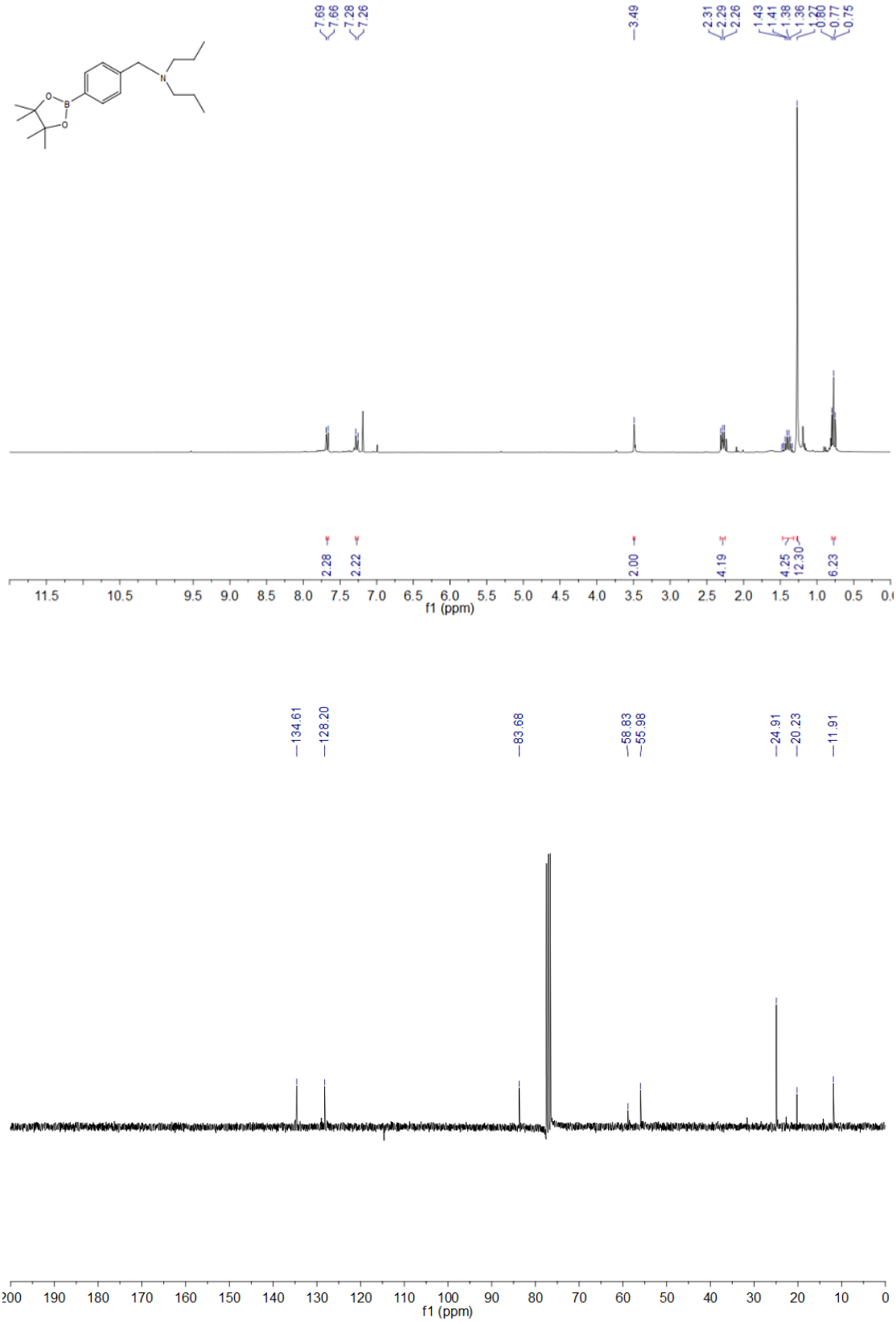


Entry 4 Table 2.19 Compound 2.26

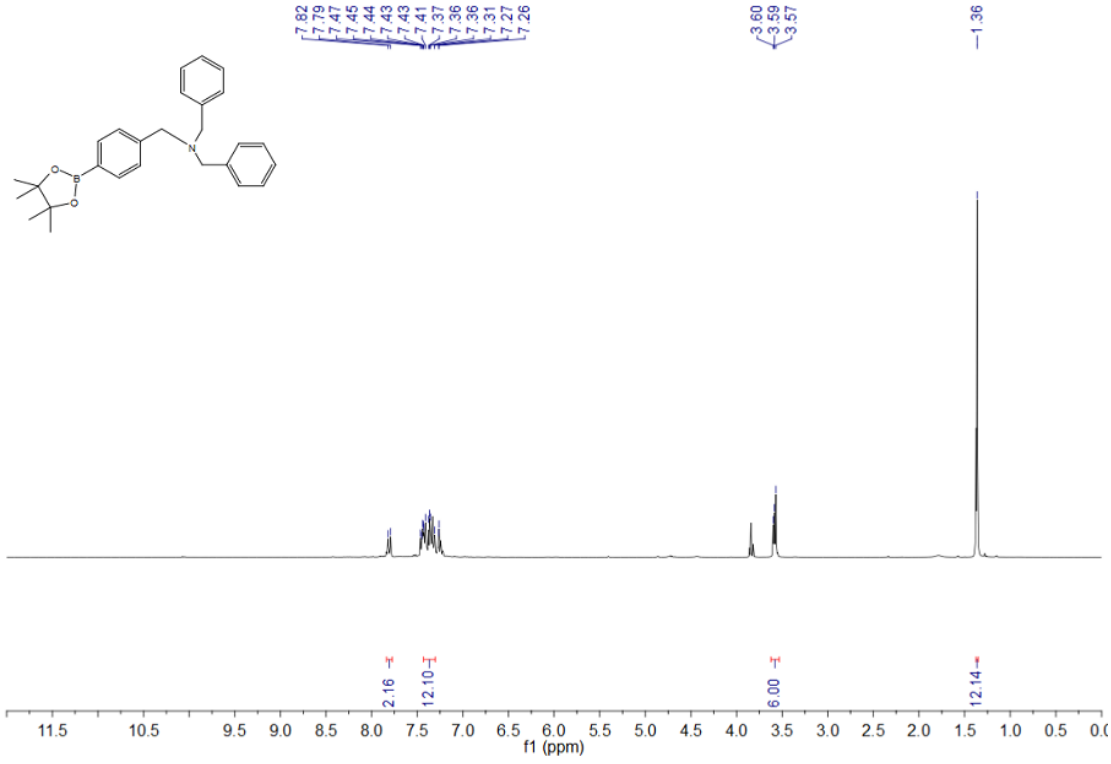


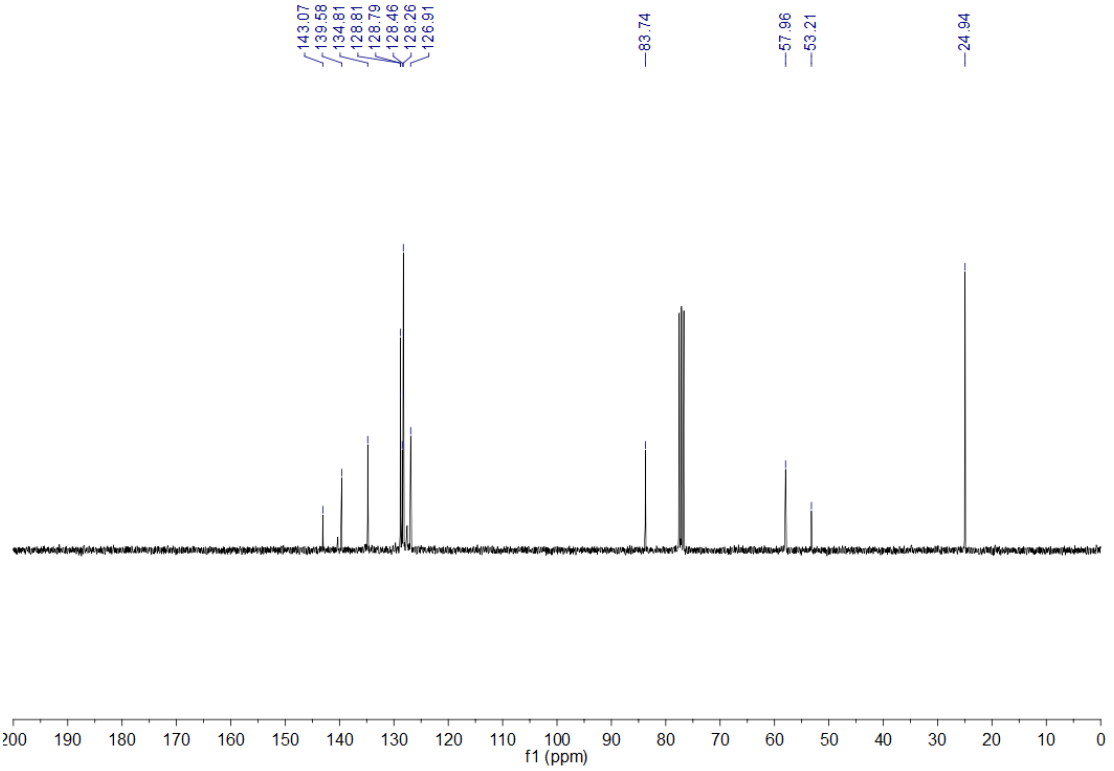


Entry 5 Table 2.19 Compound 2.27

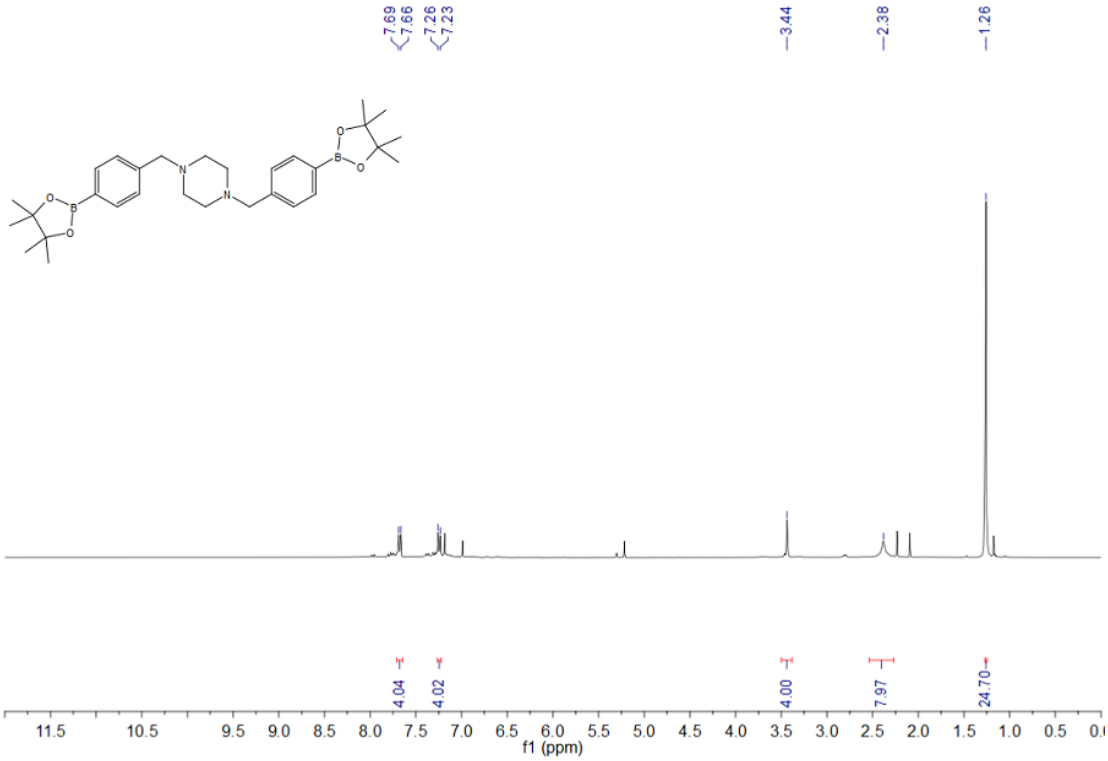


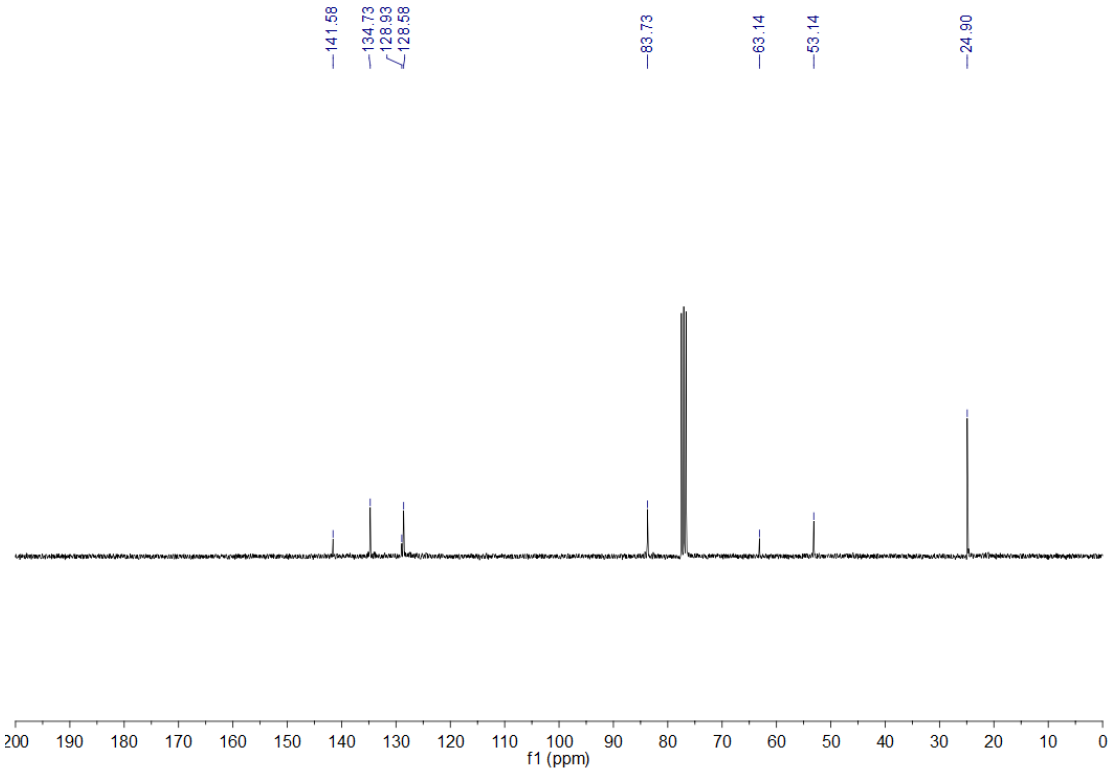
Entry 6 Table 2.19 Compound 2.28



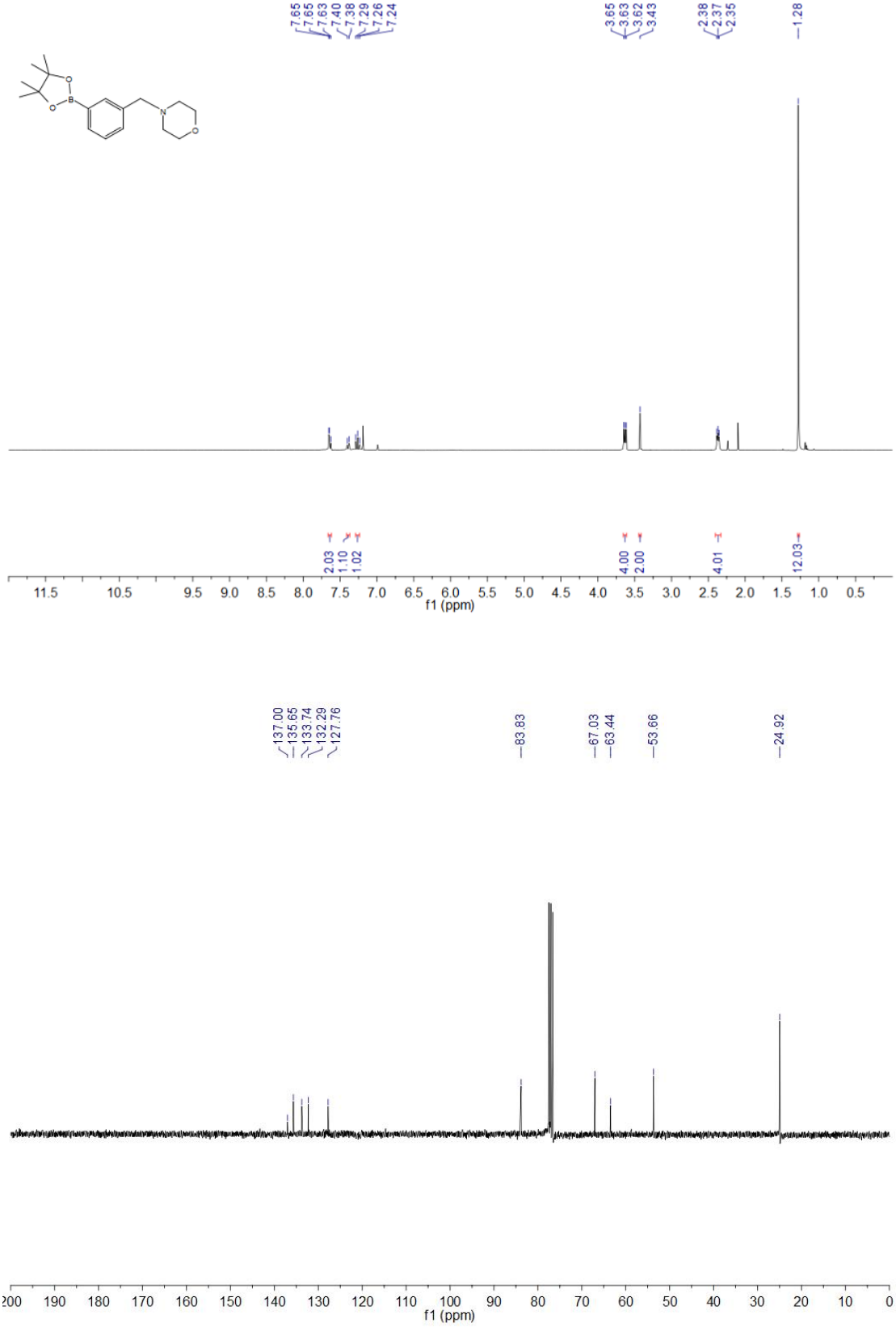


Entry 7 Table 2.19 Compound 2.29

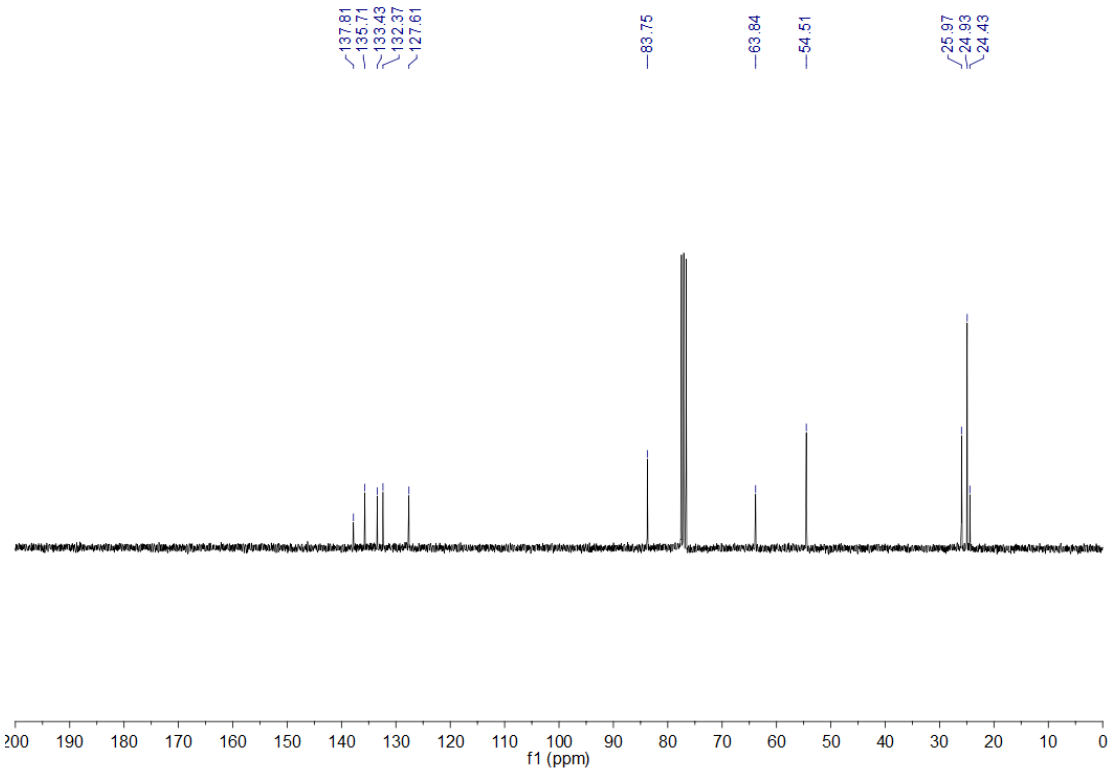




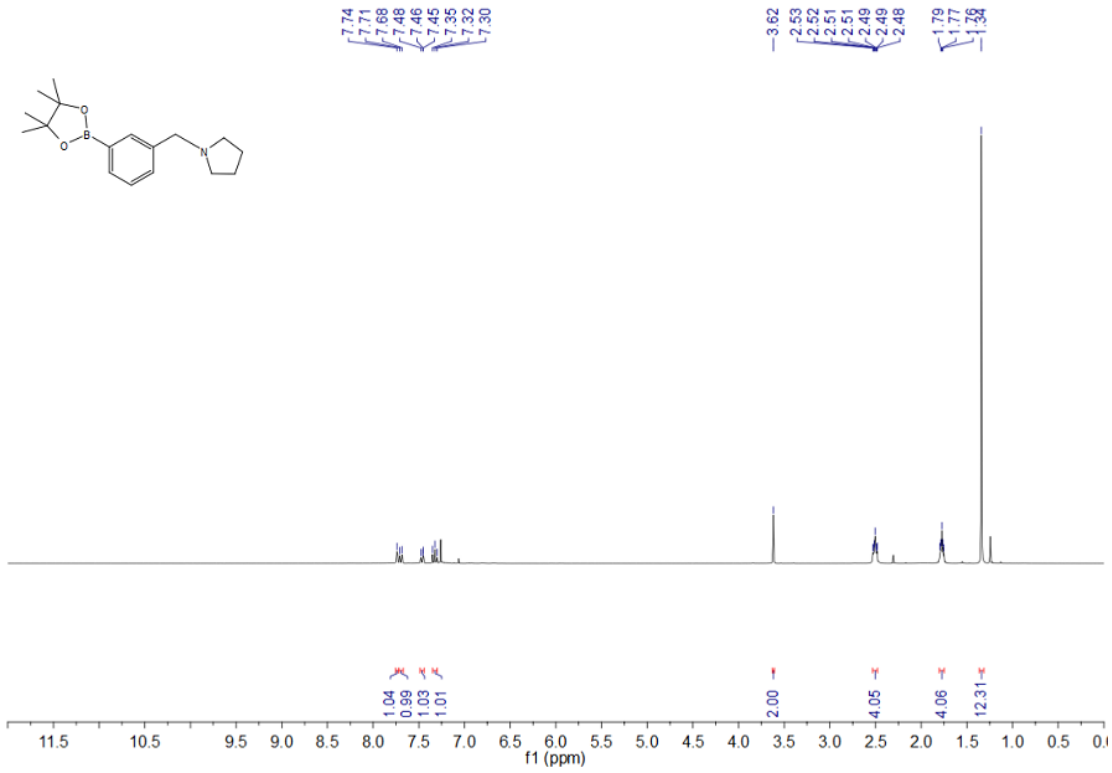
Entry 1 Table 2.20 Compound 2.9

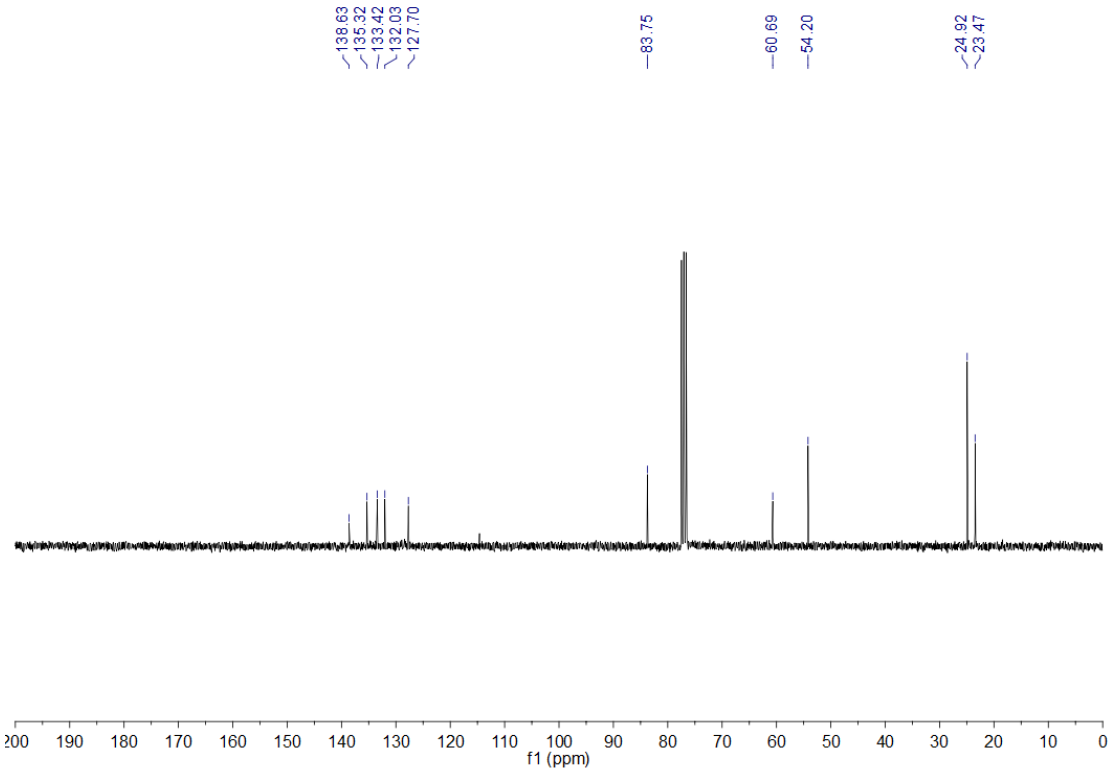


Entry 2 Table 2.20 Compound 2.30

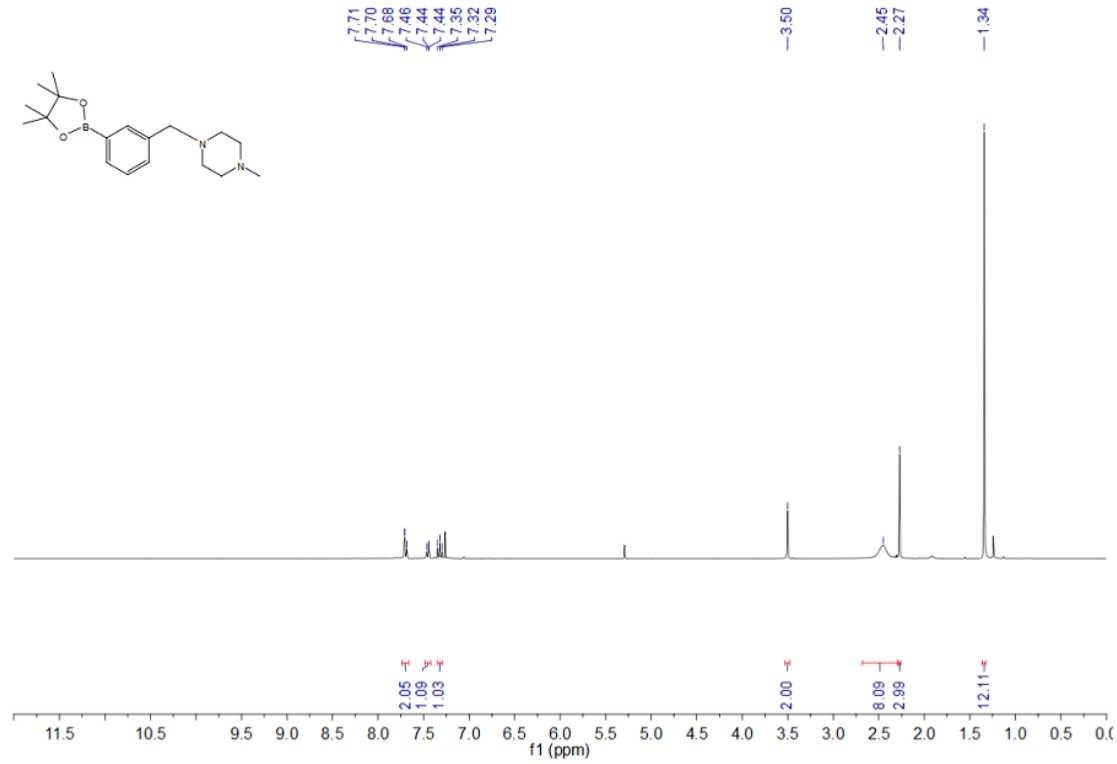


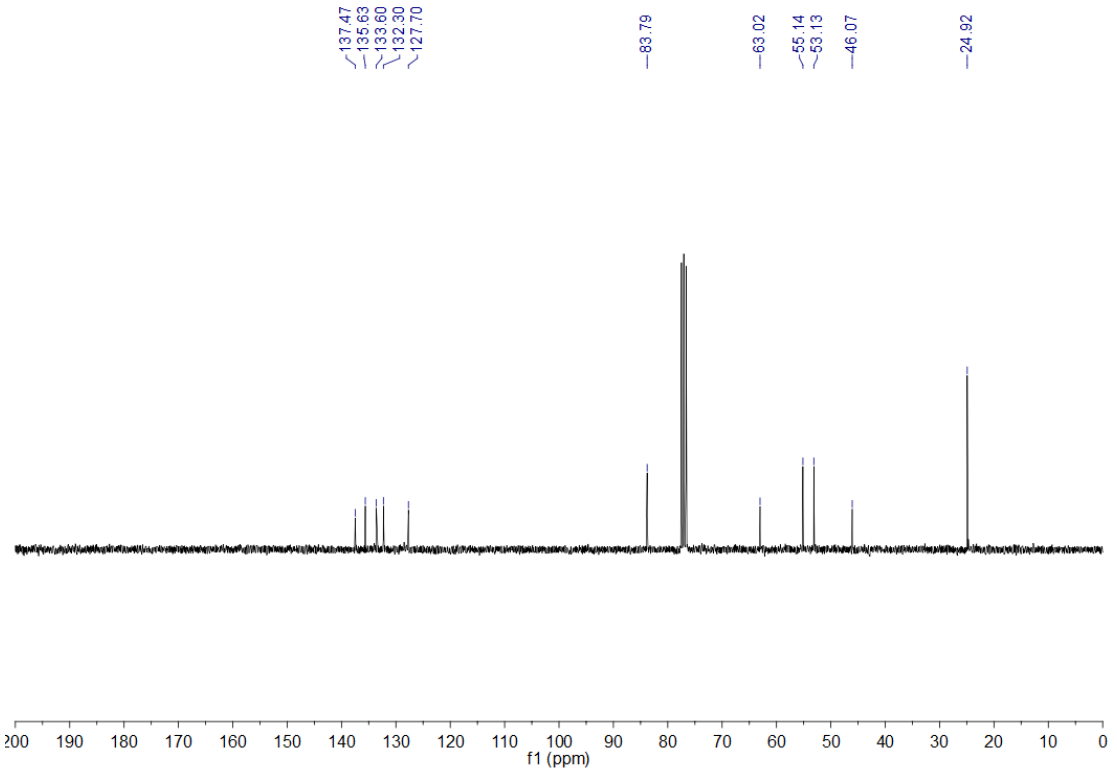
Entry 3 Table 2.20 Compound 2.31



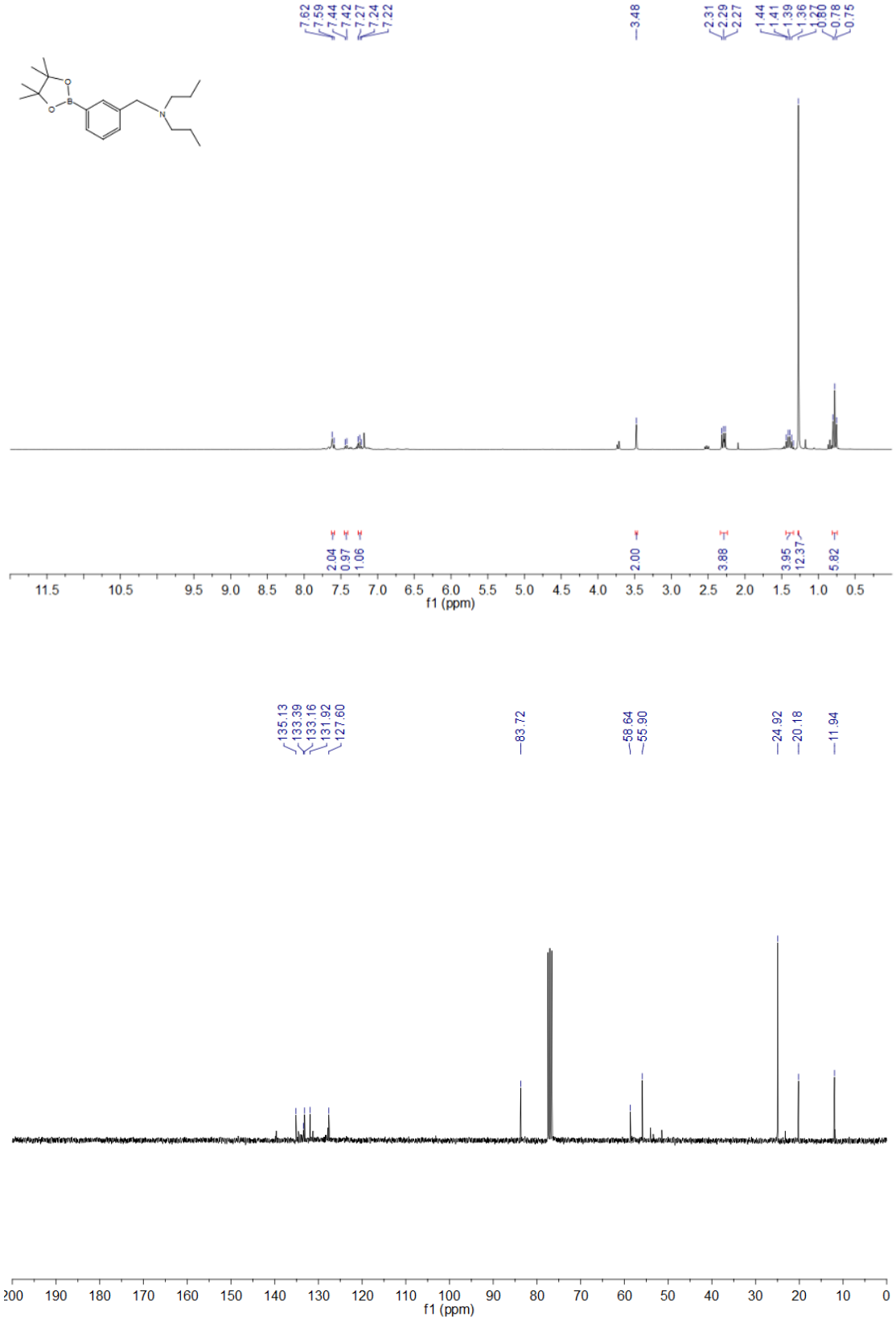


Entry 4 Table 2.20 Compound 2.32

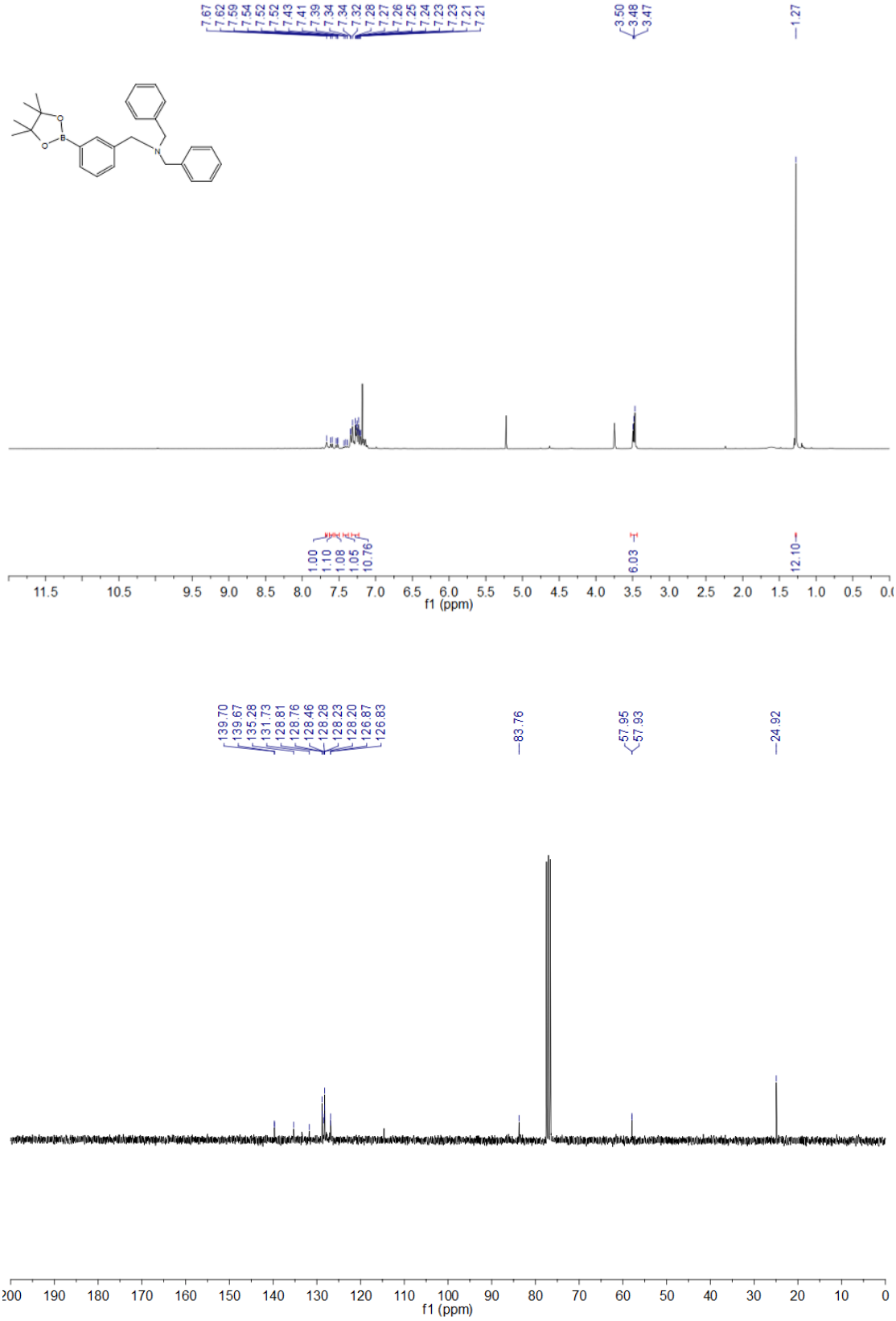




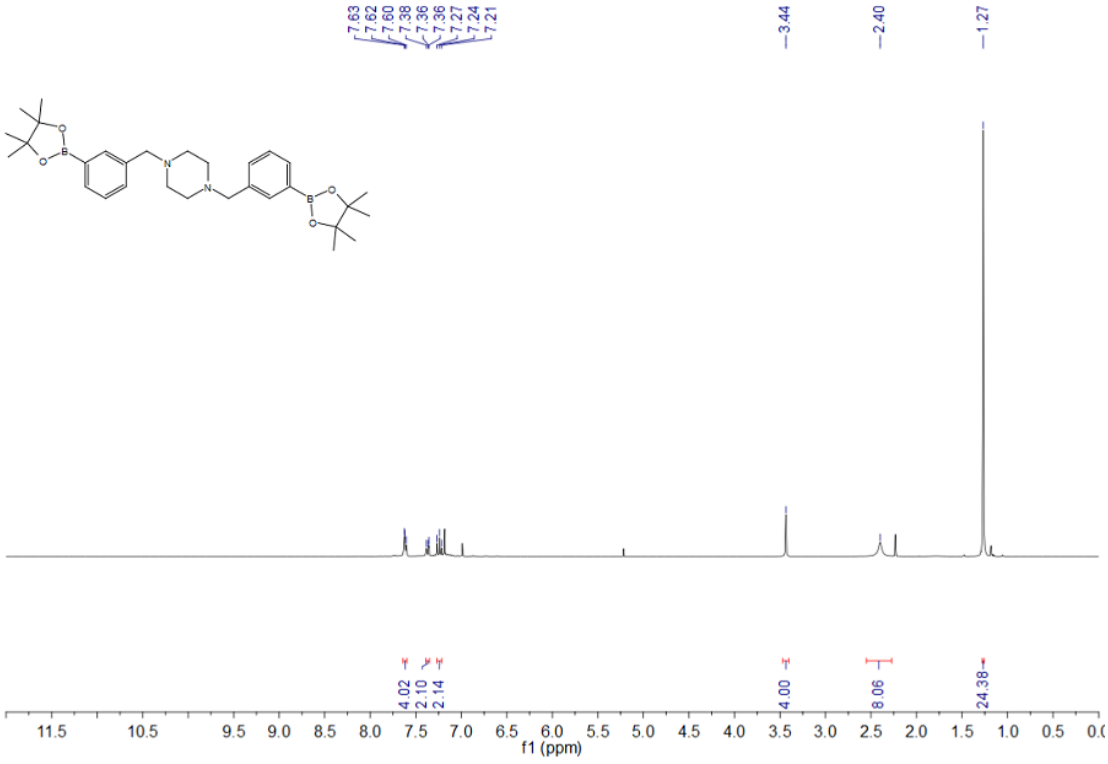
Entry 5 Table 2.20 Compound 2.33

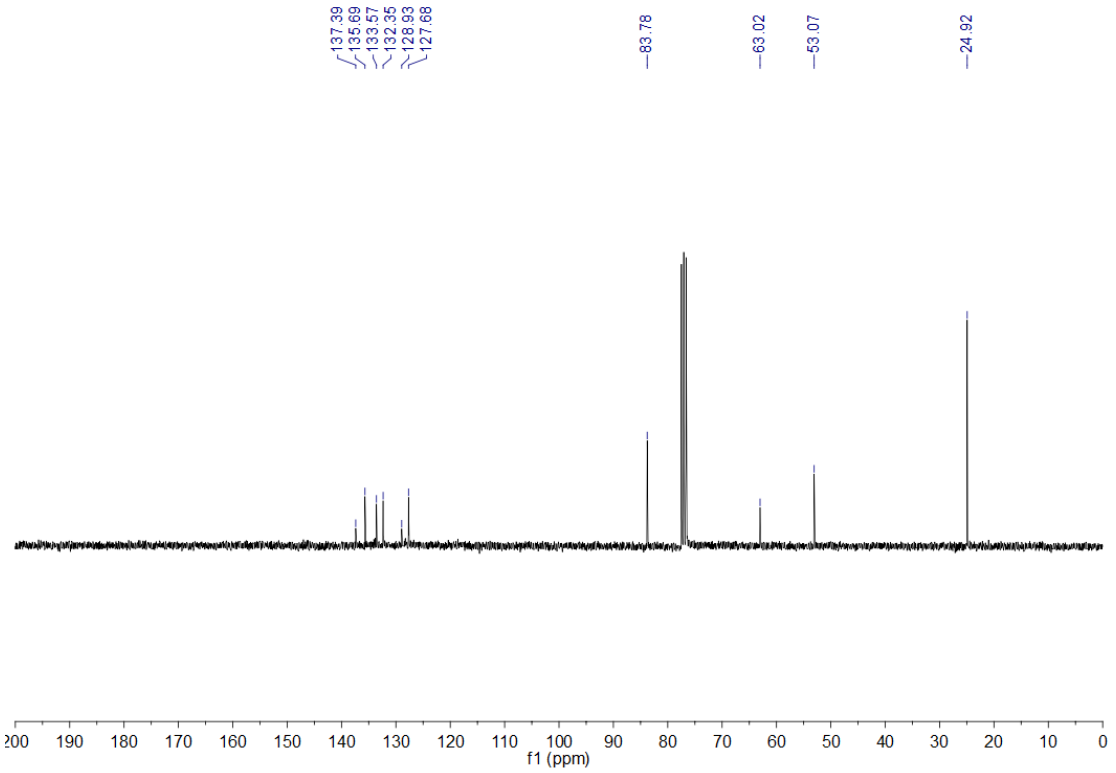


Entry 6 Table 2.20 Compound 2.34

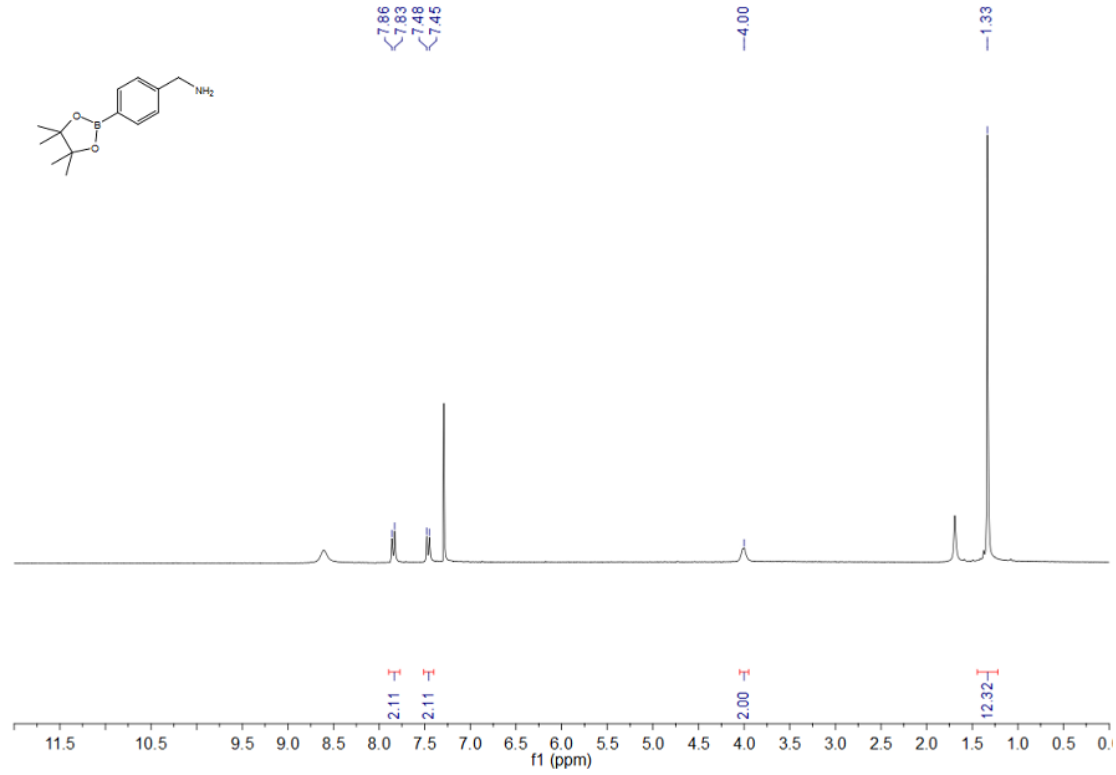


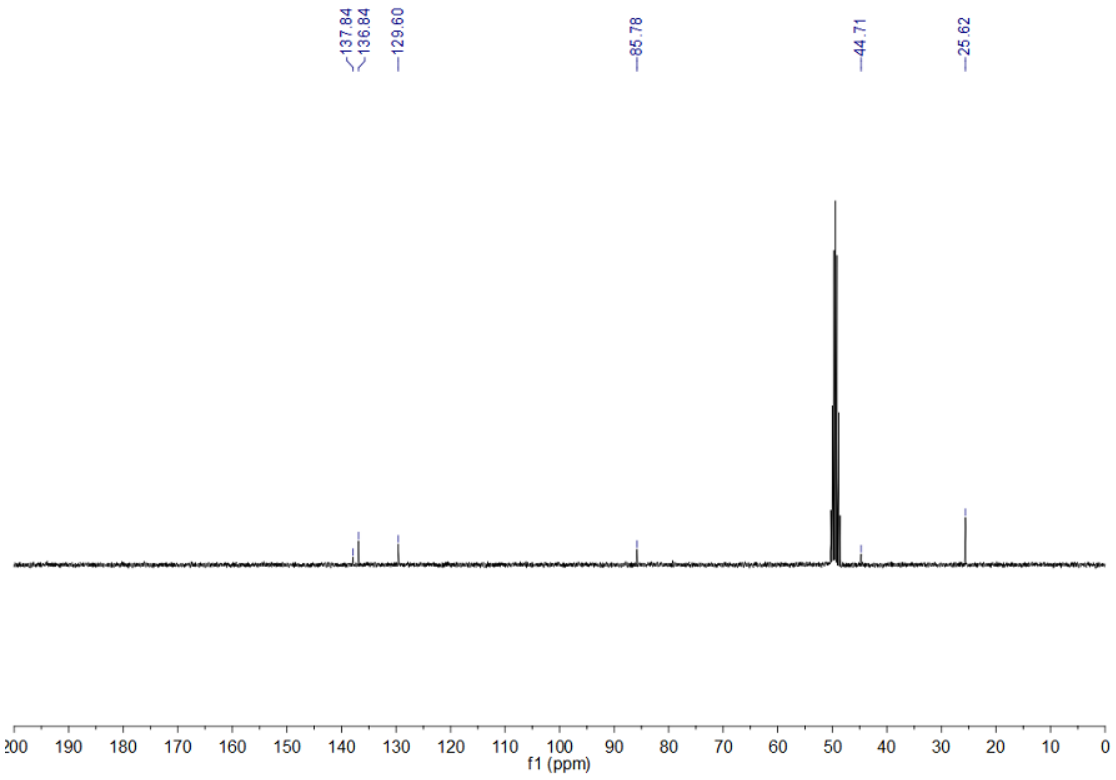
Entry 7 Table 2.20 Compound 2.35



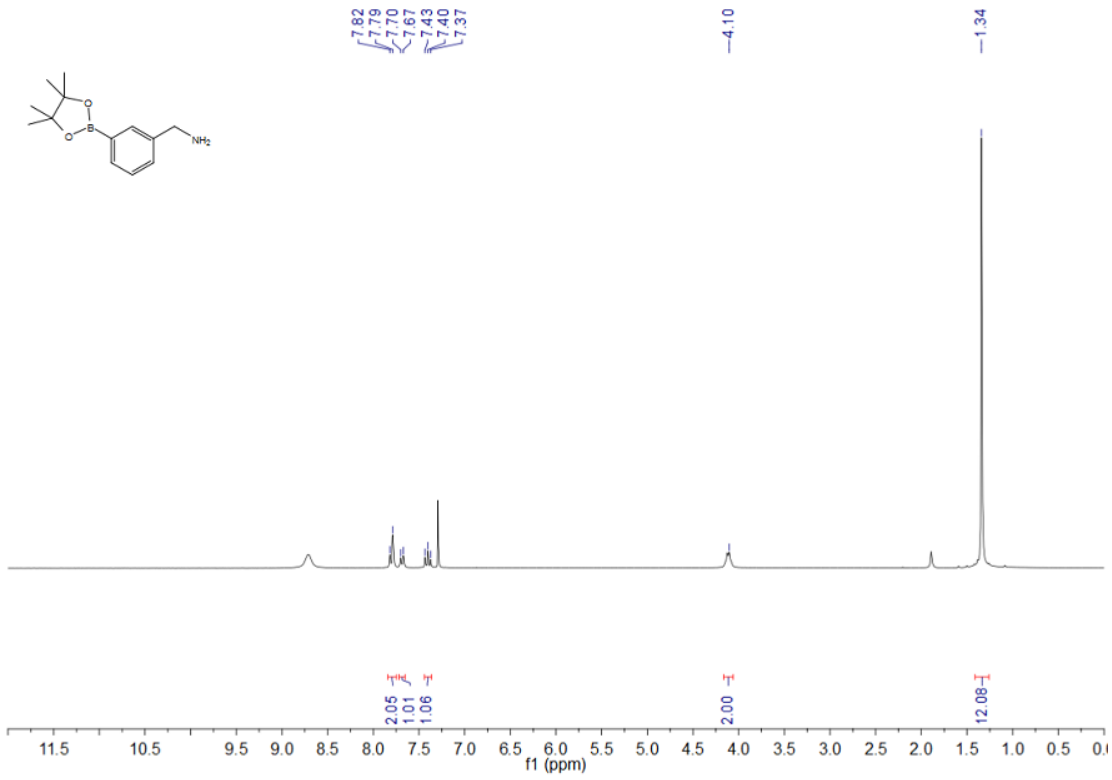


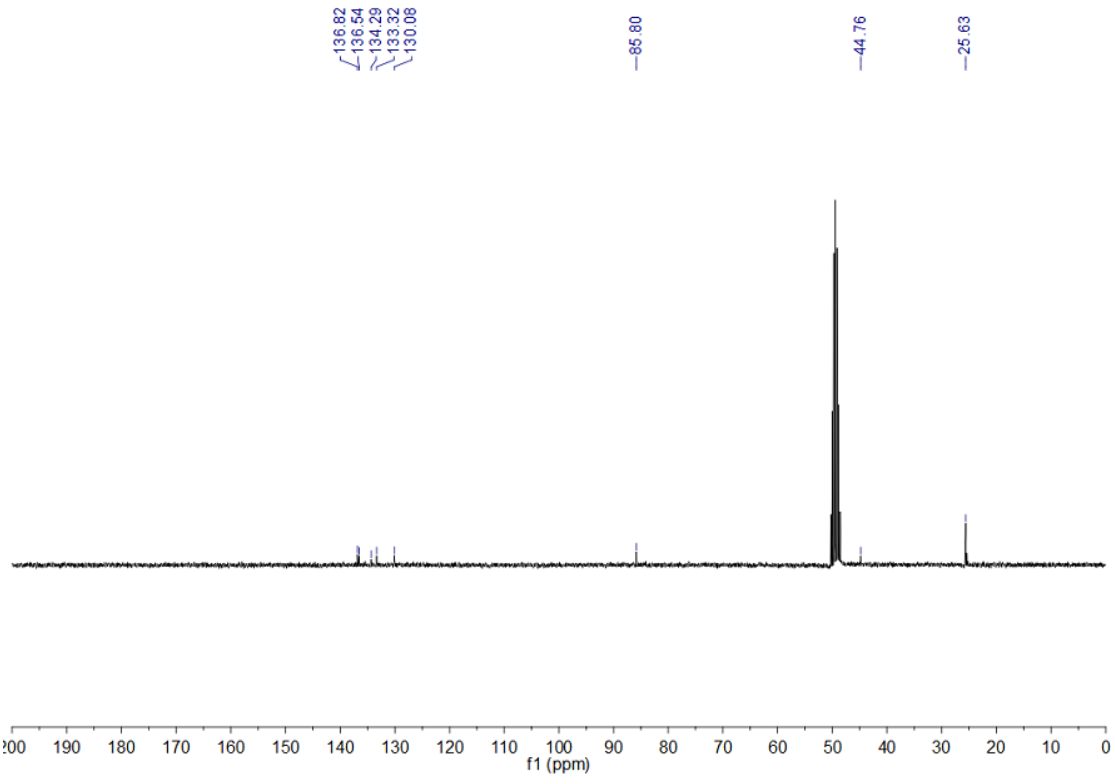
Compound 2.46



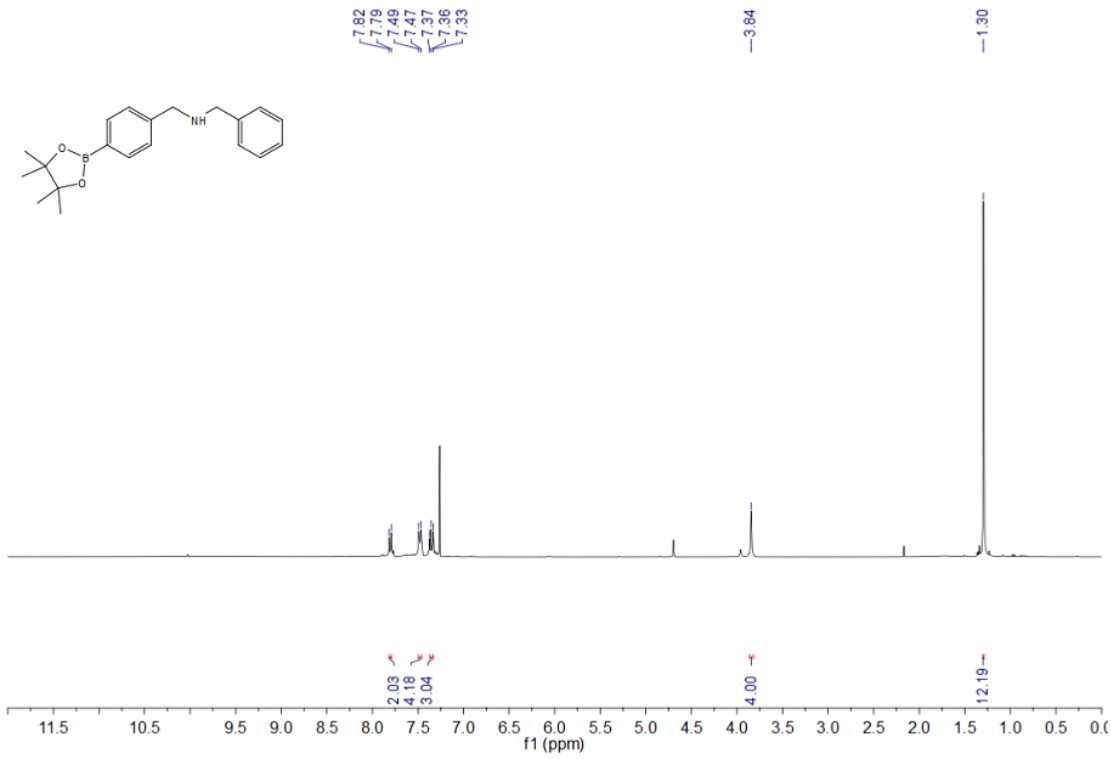


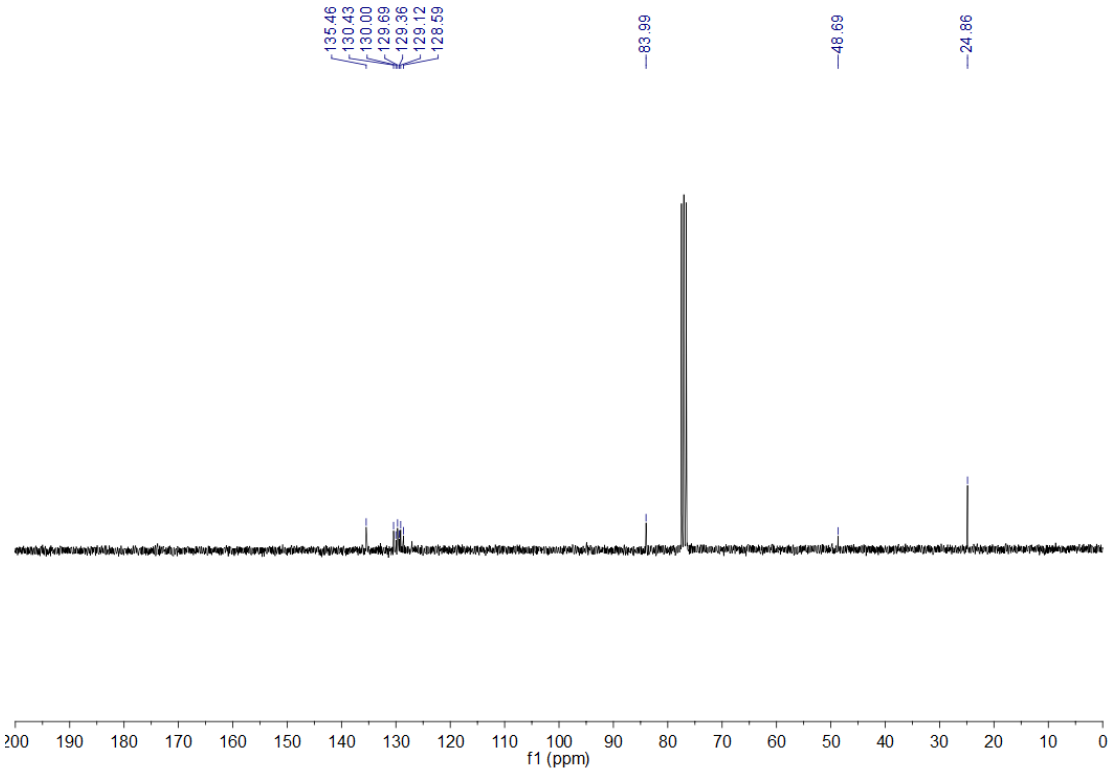
Compound 2.50



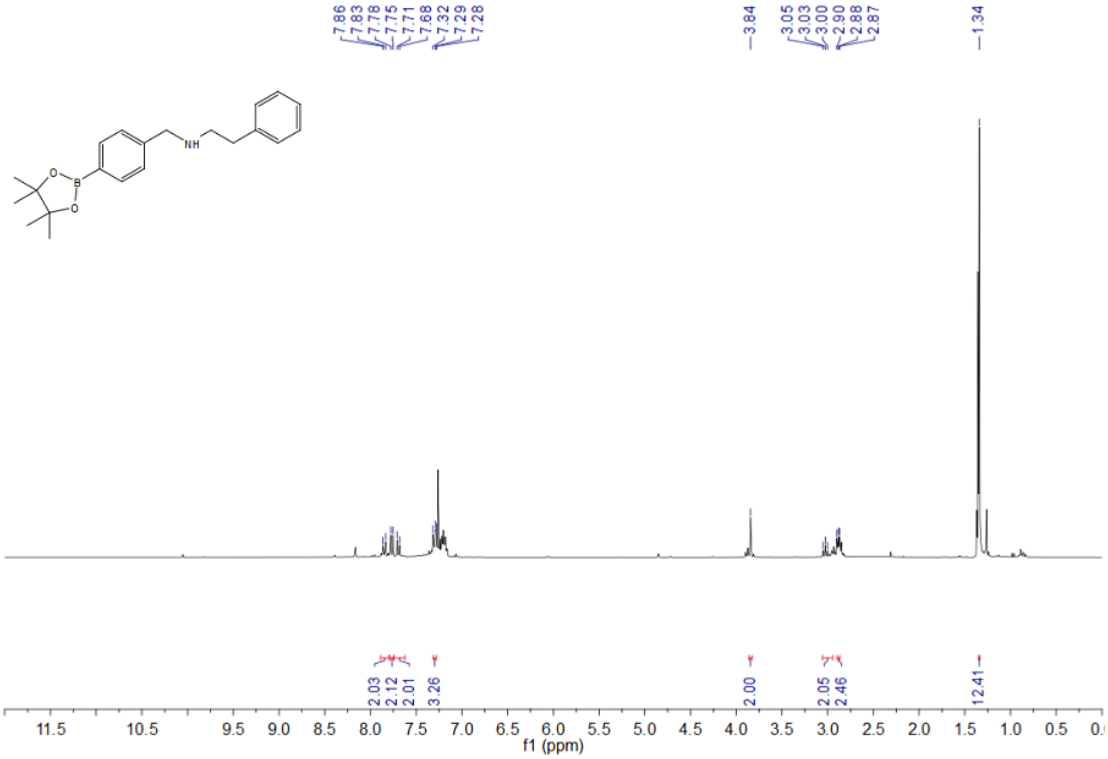


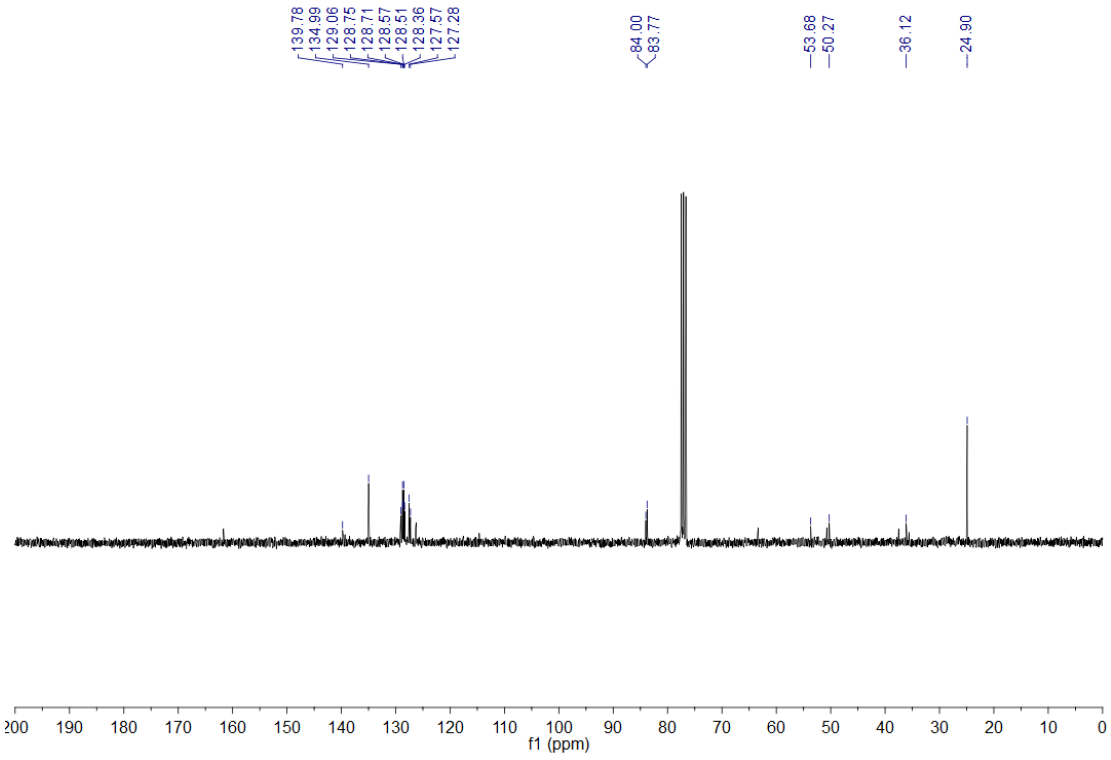
Entry 1 Table 2.21 Compound 2.47



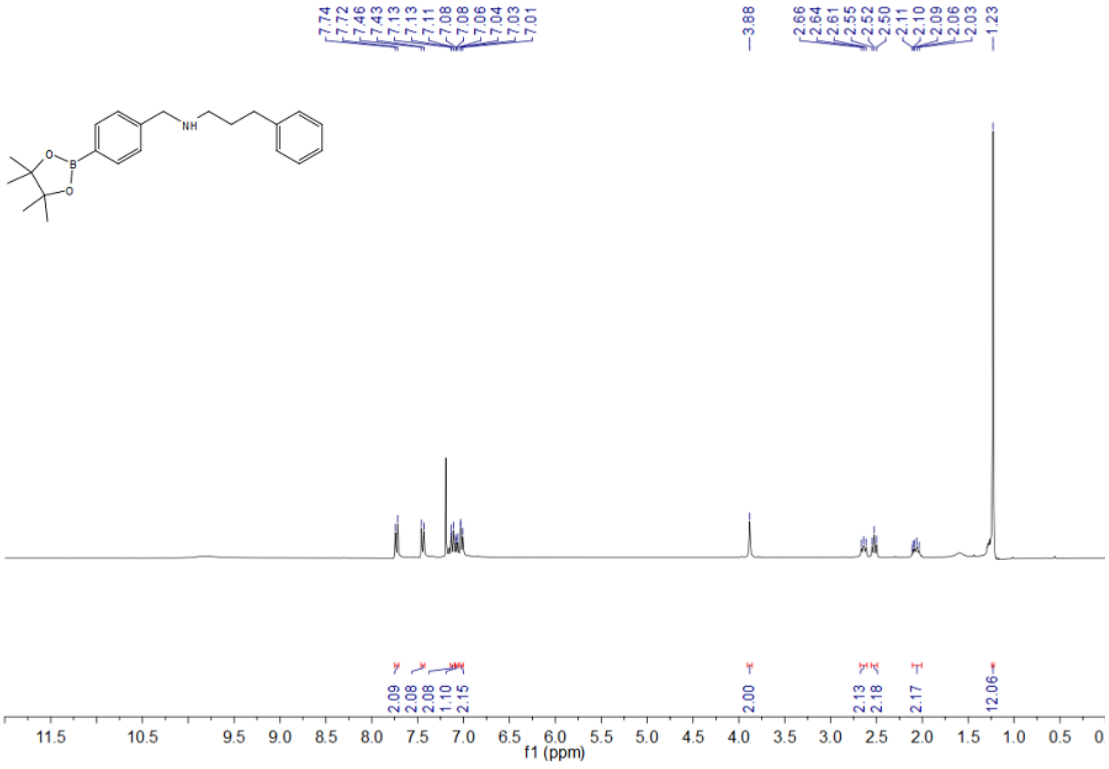


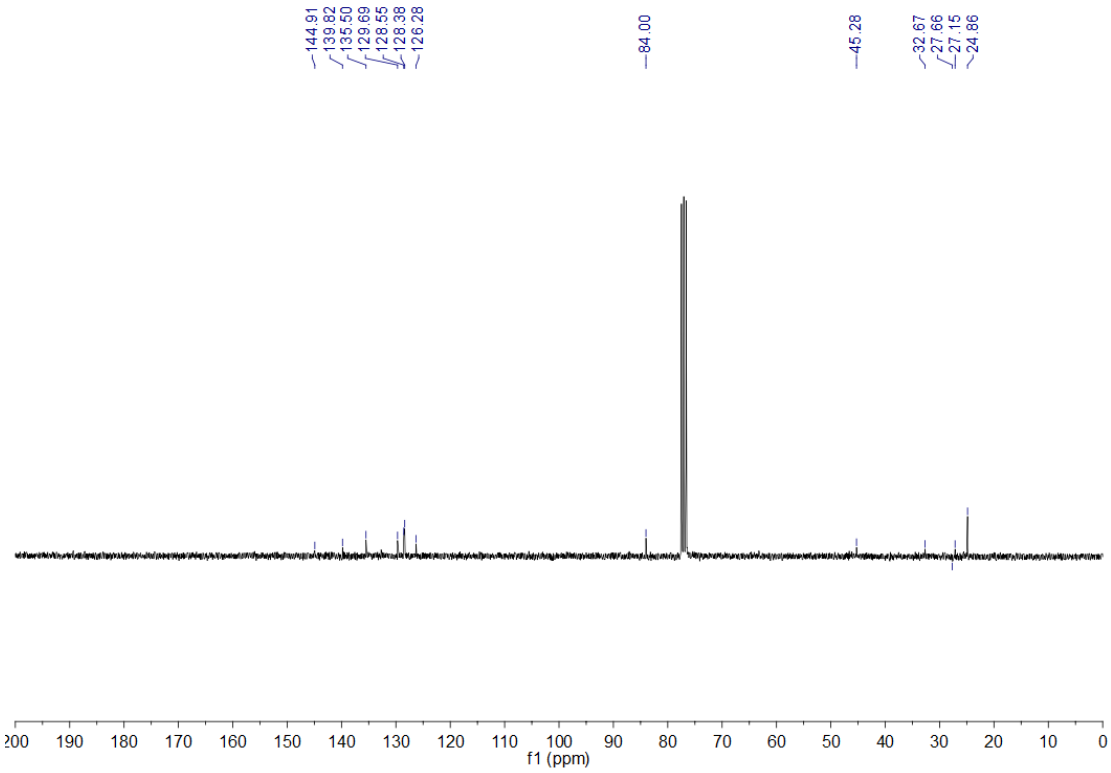
Entry 2 Table 2.21 Compound 2.48



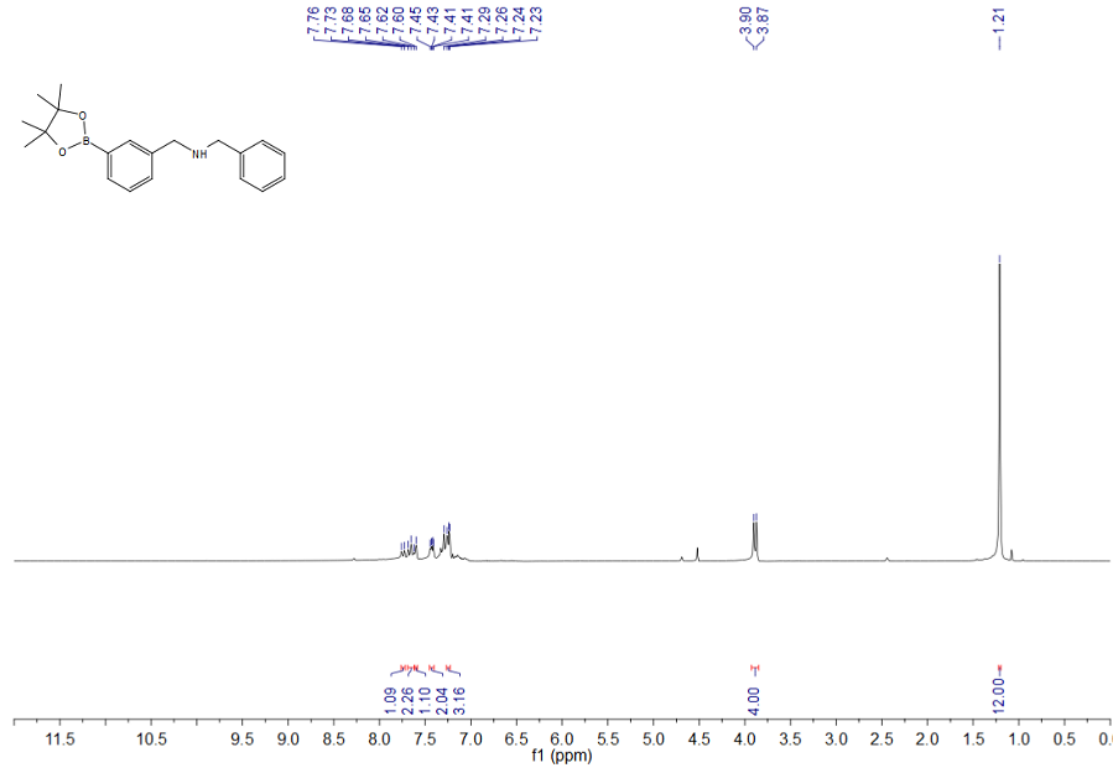


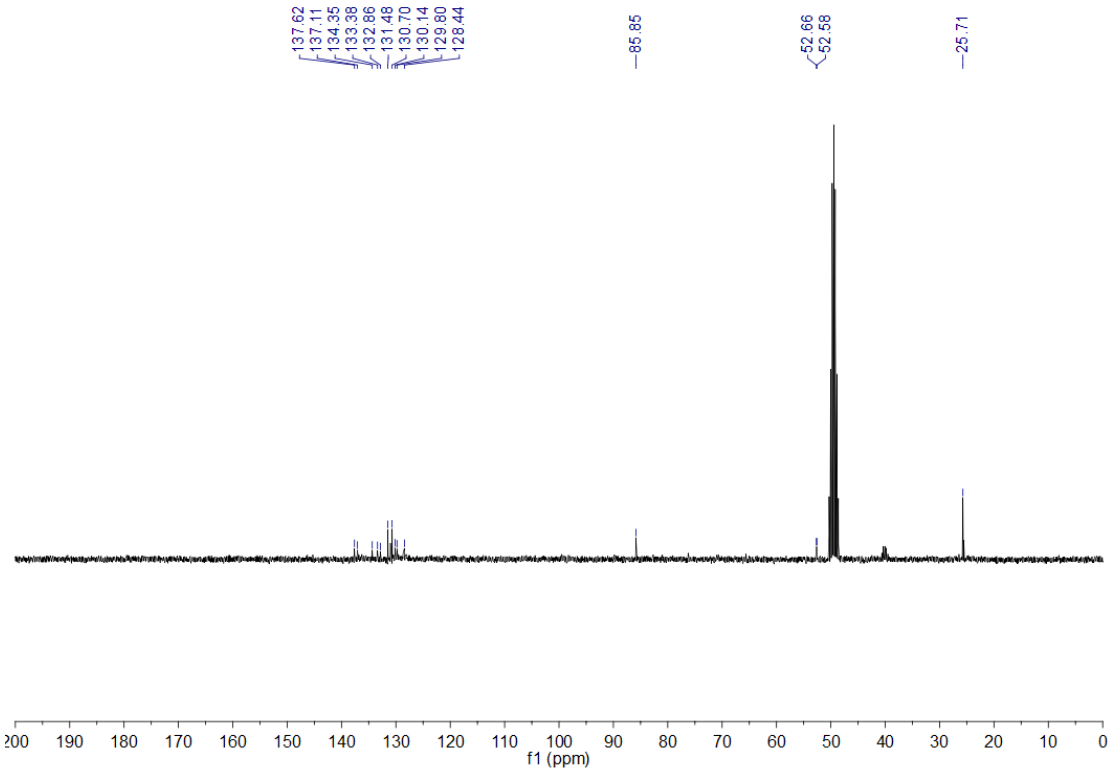
Entry 3 Table 2.21 Compound 2.49



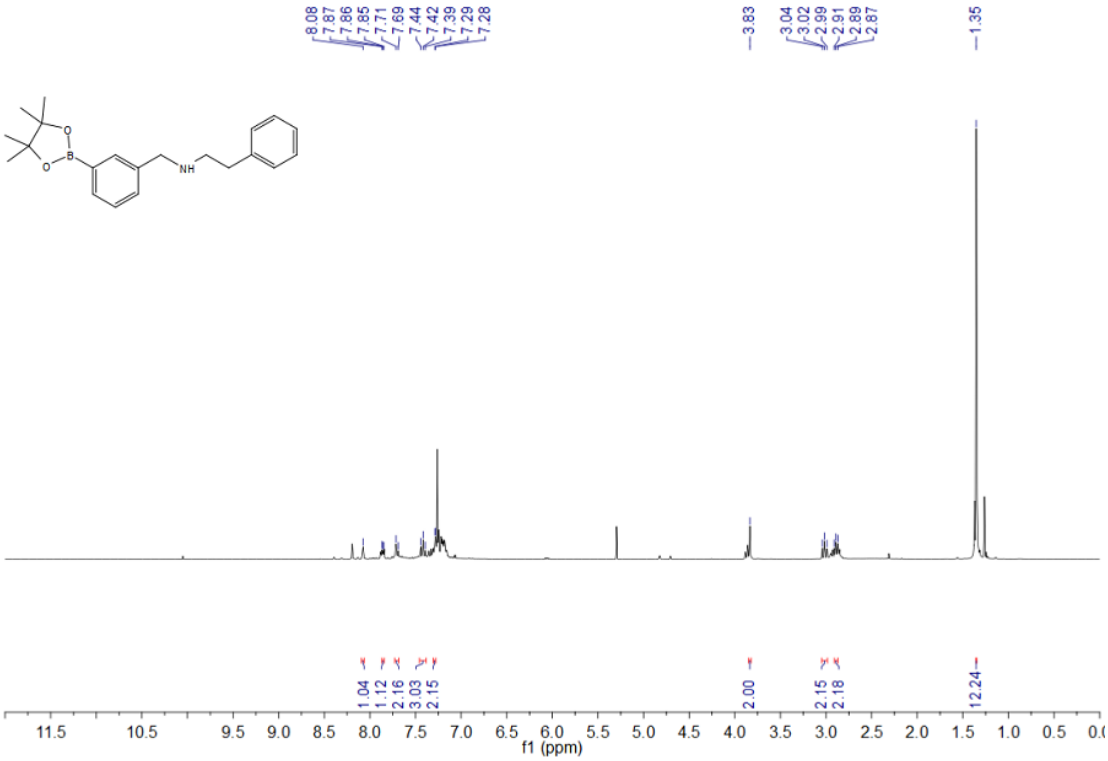


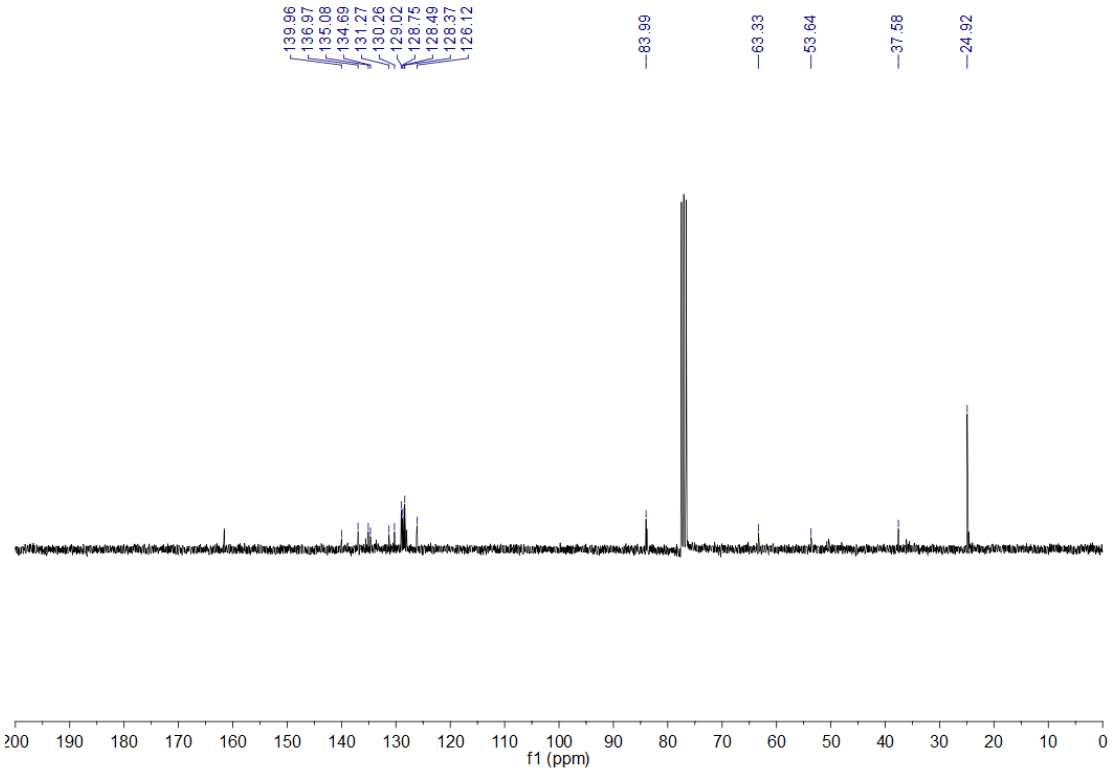
Entry 1 Table 2.22 Compound 2.51



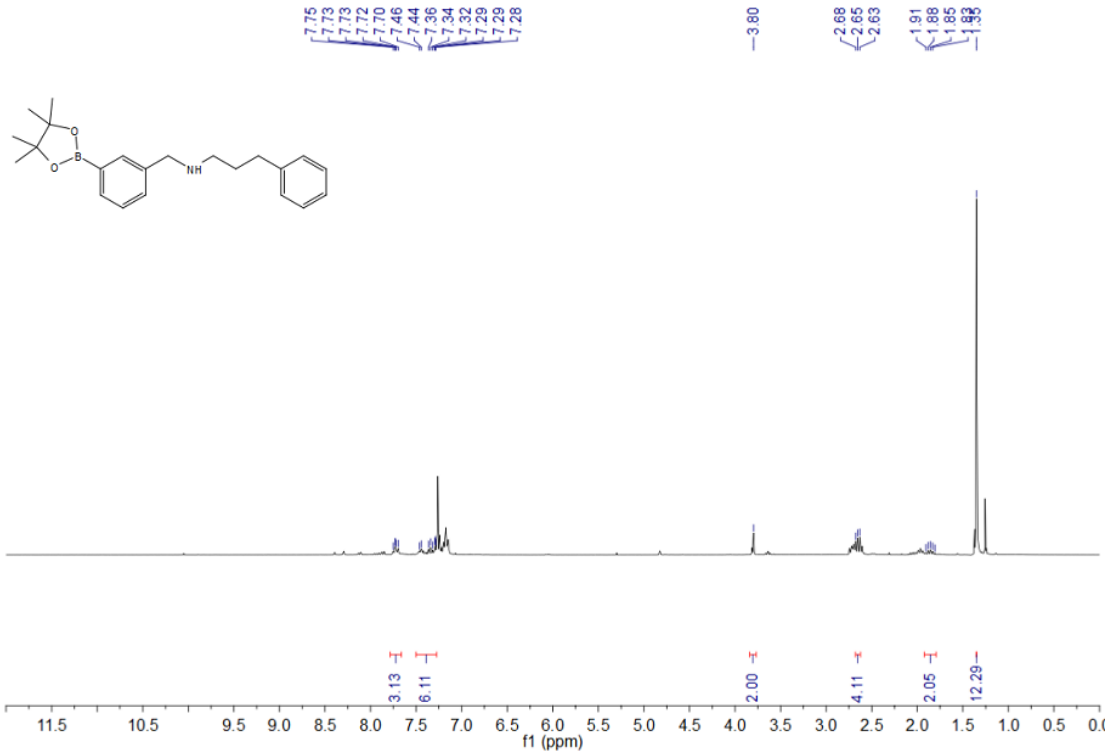


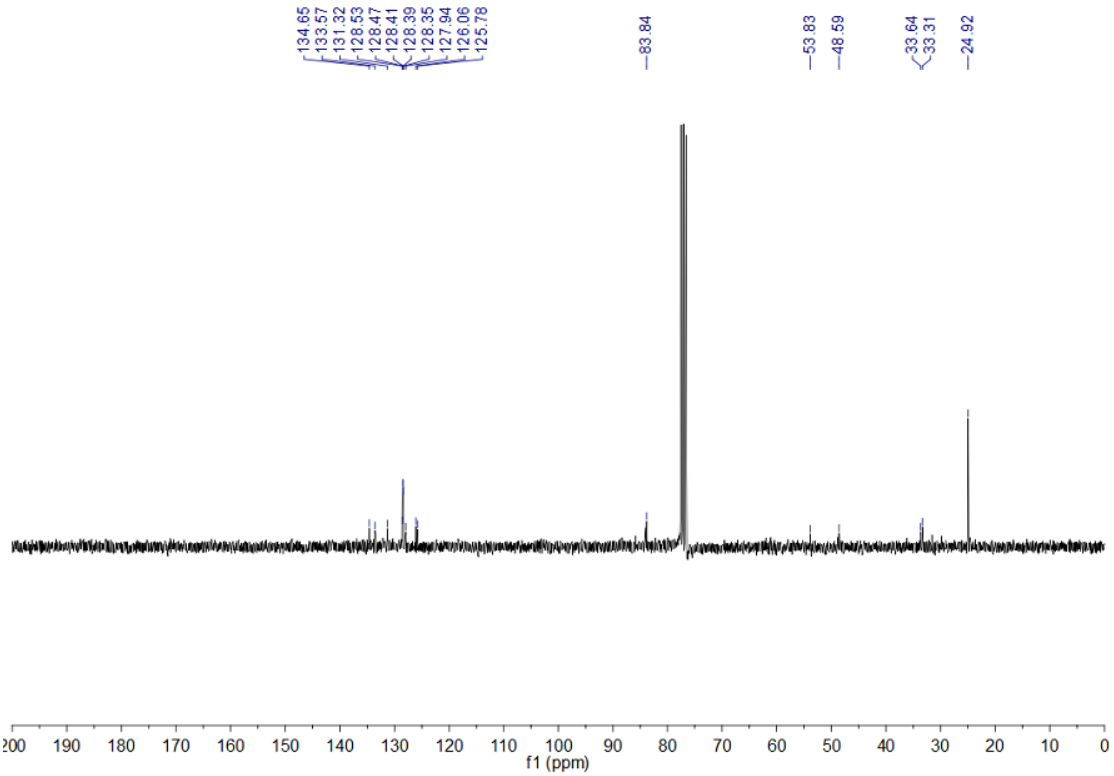
Entry 2 Table 2.22 Compound 2.52



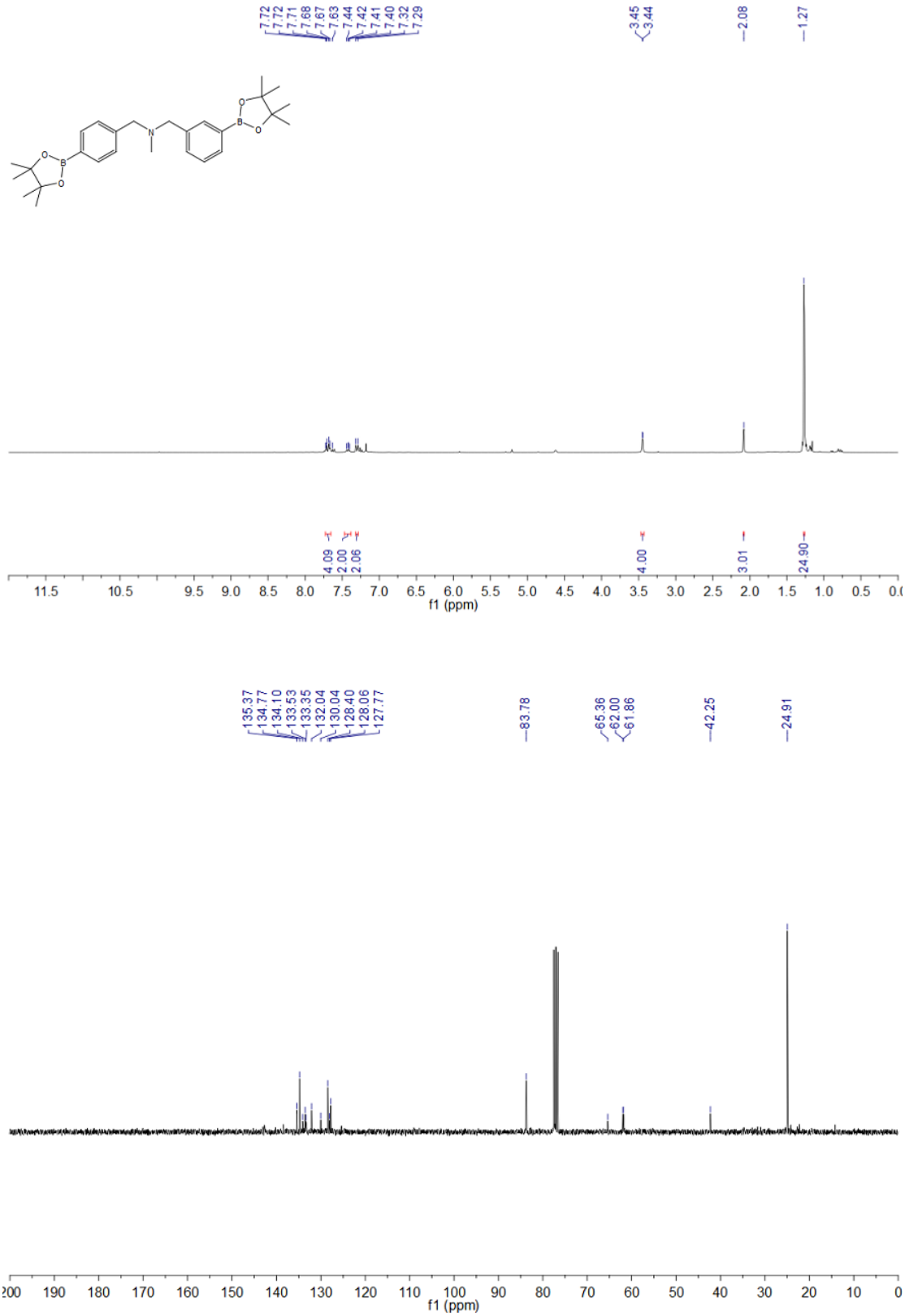


Entry 3 Table 2.22 Compound 2.53

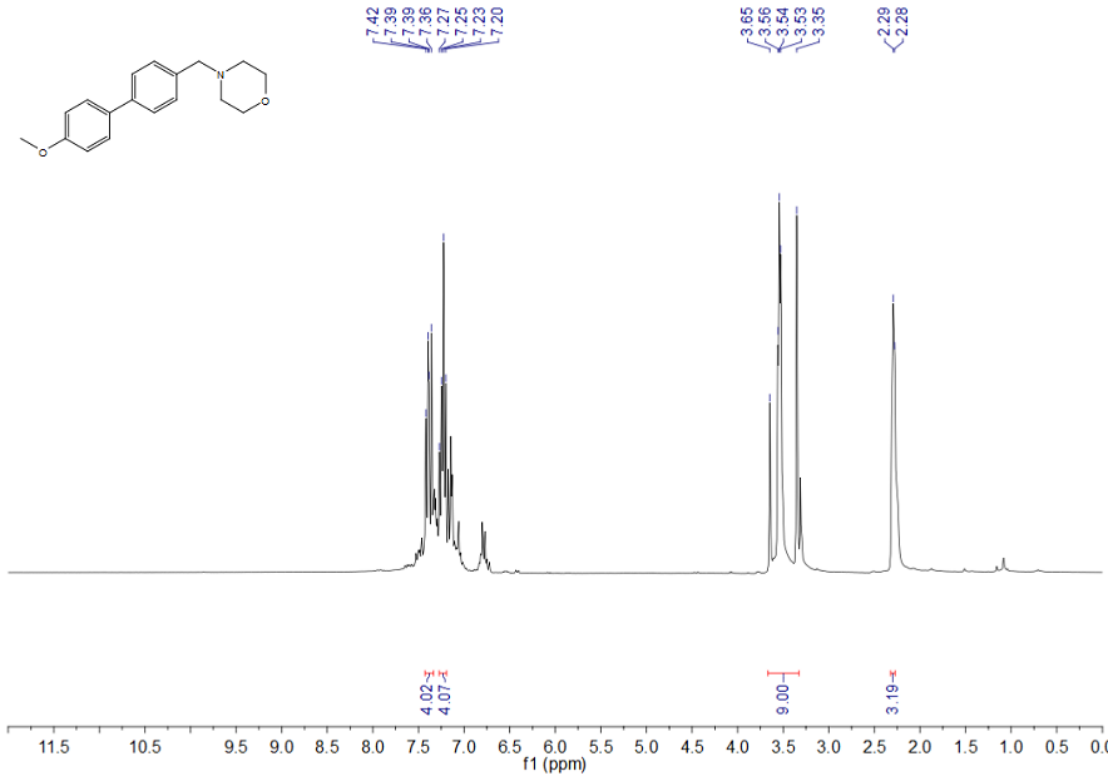


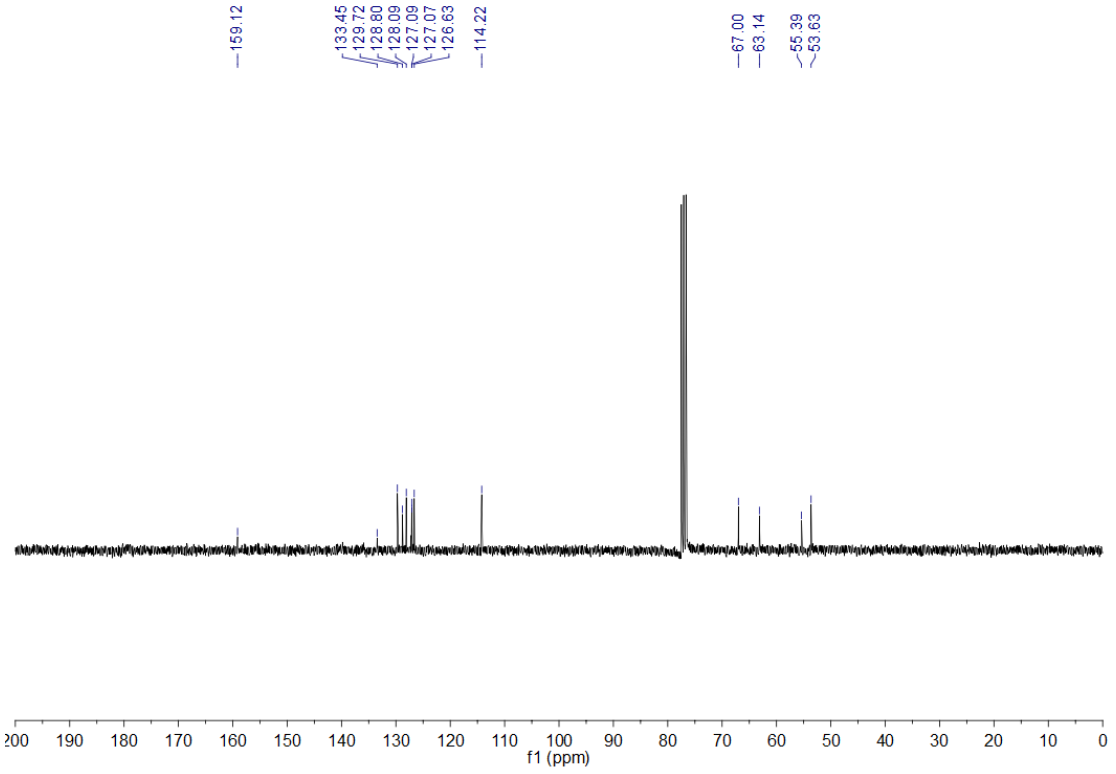


Compound 2.55

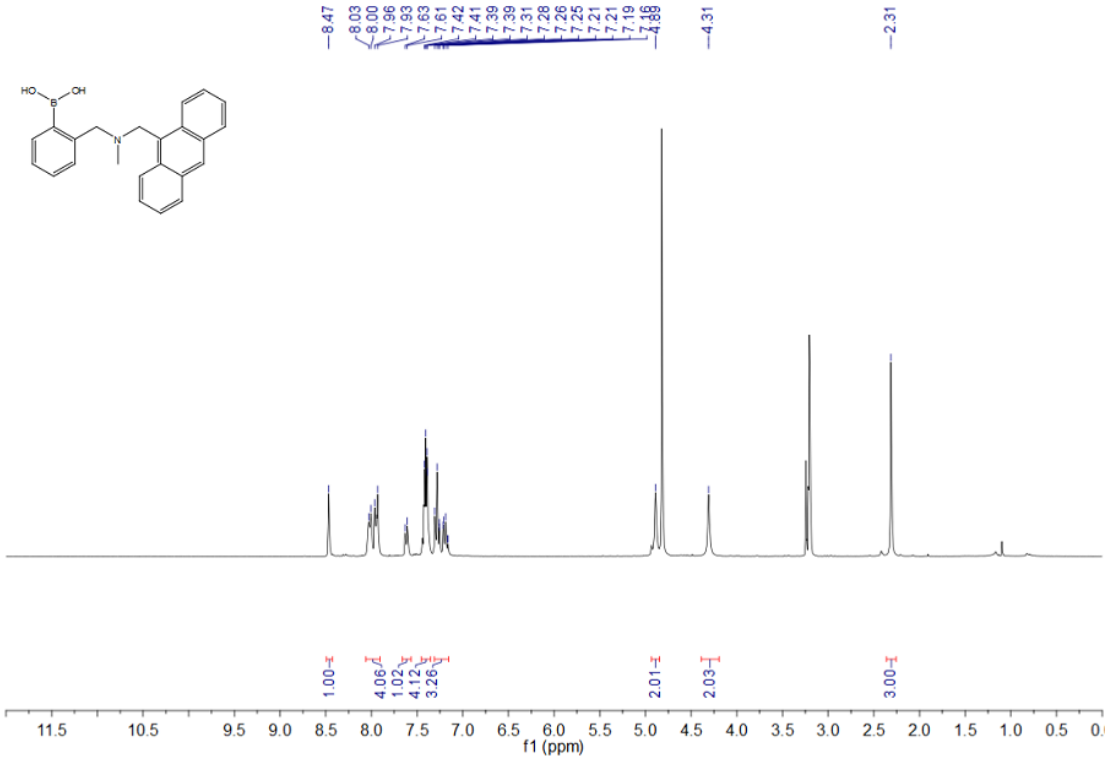


Compound 2.56





Compound 3.2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7.39
7.39
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7.28
7.26
7.25
7.21
7.21
7.19
7.16
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4.31
2.31
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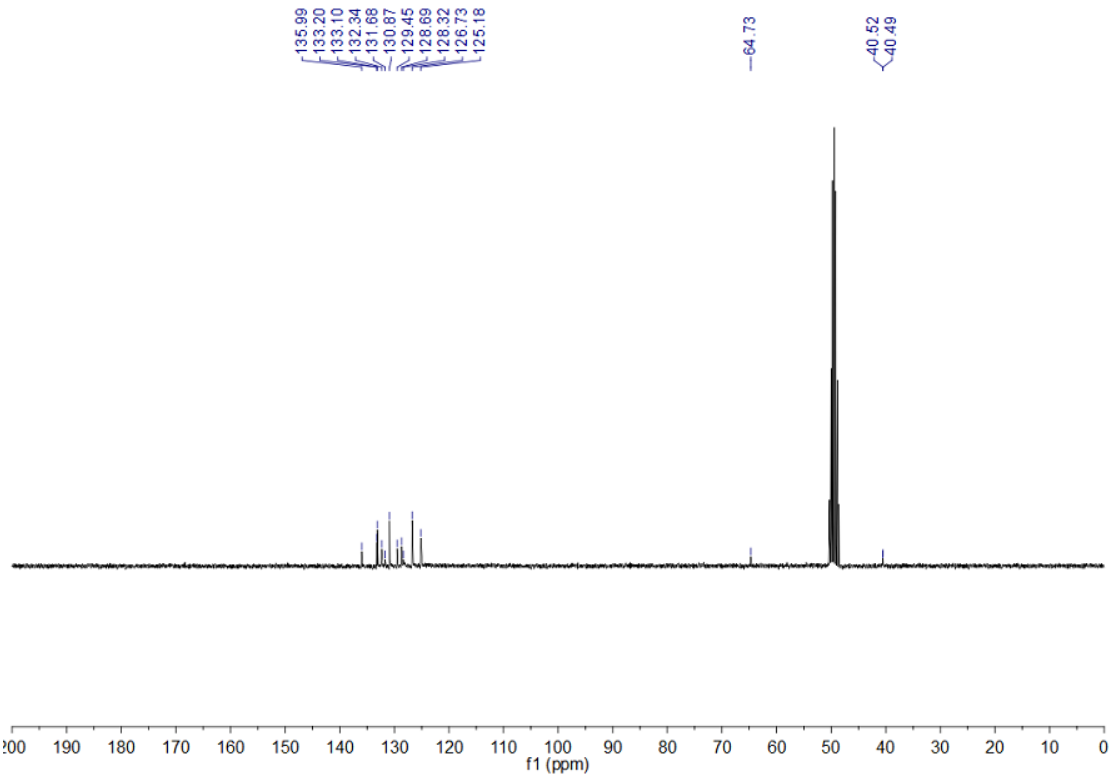
4.06
1.02
4.12
3.26
2.01
2.03
3.00
f1 (ppm)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131.68
130.87
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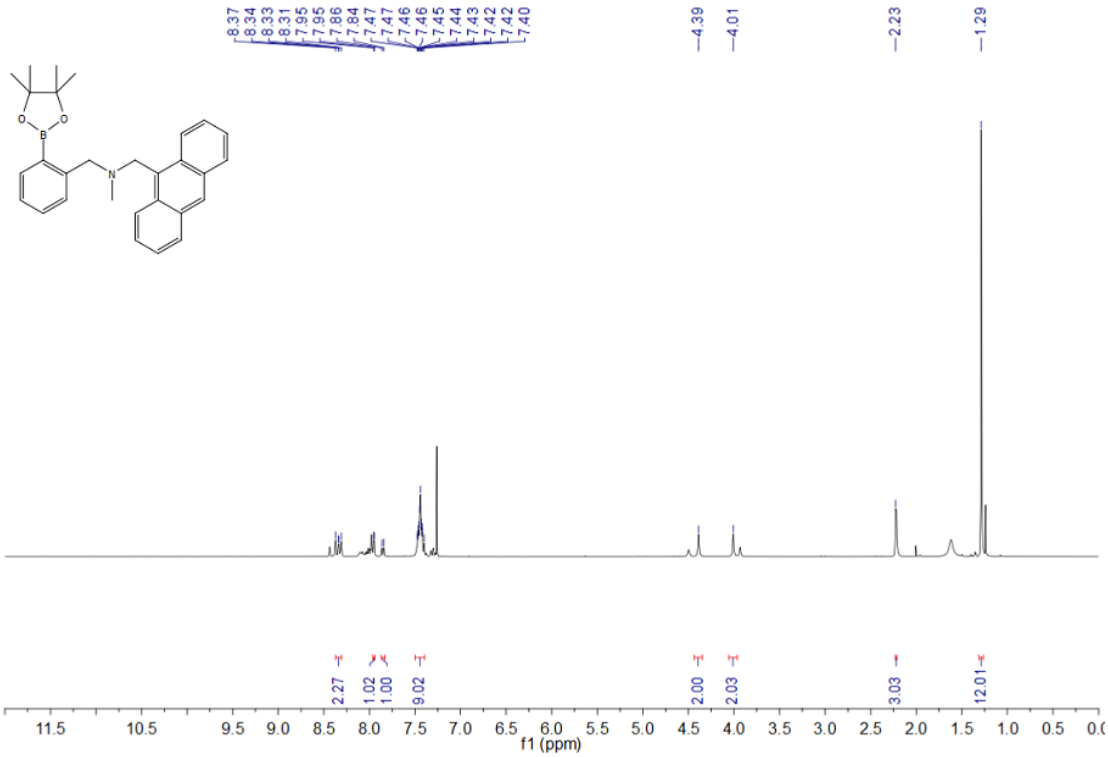
128.69
128.32
126.73
125.18
64.73
40.52
40.49
f1 (ppm)

Compound 3.5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7.42
7.42
7.40
4.39
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2.27
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2.03
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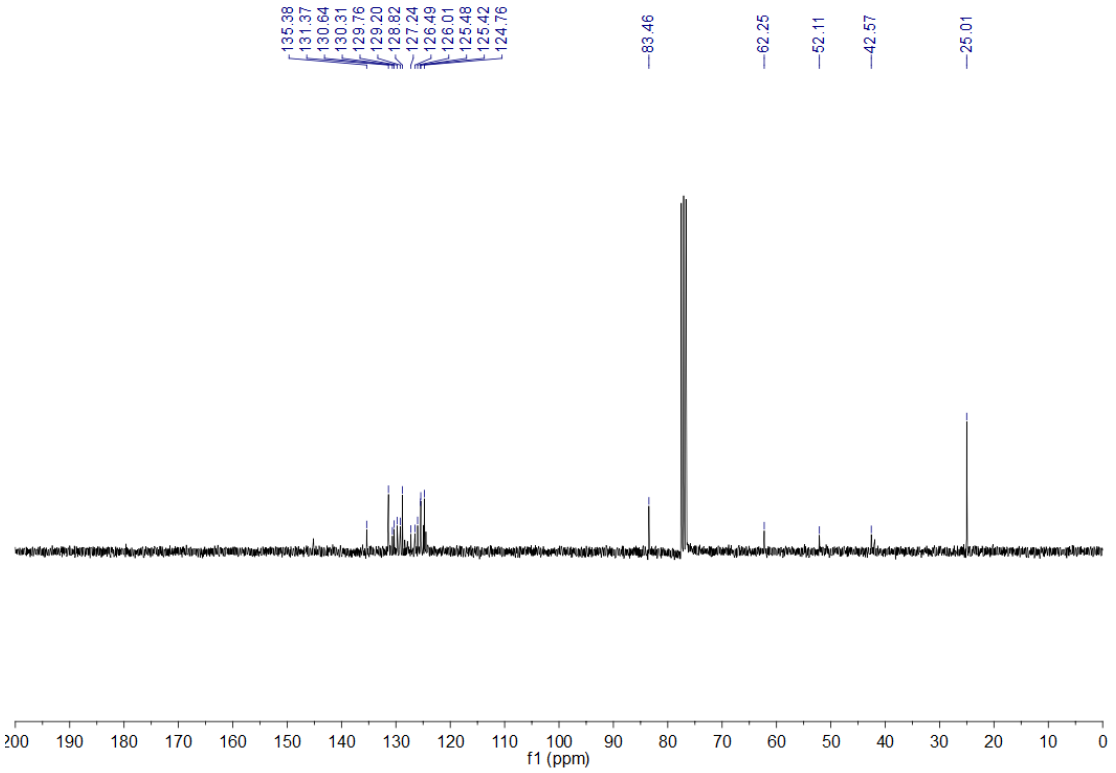
12.01
f1 (ppm)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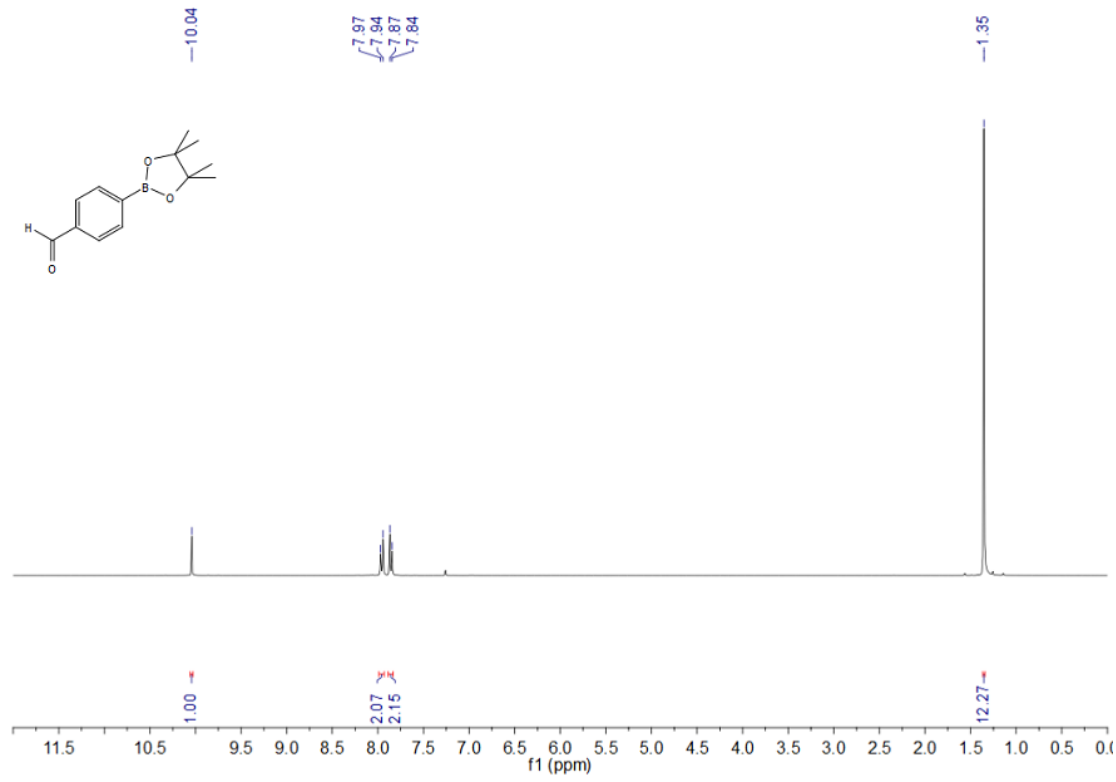
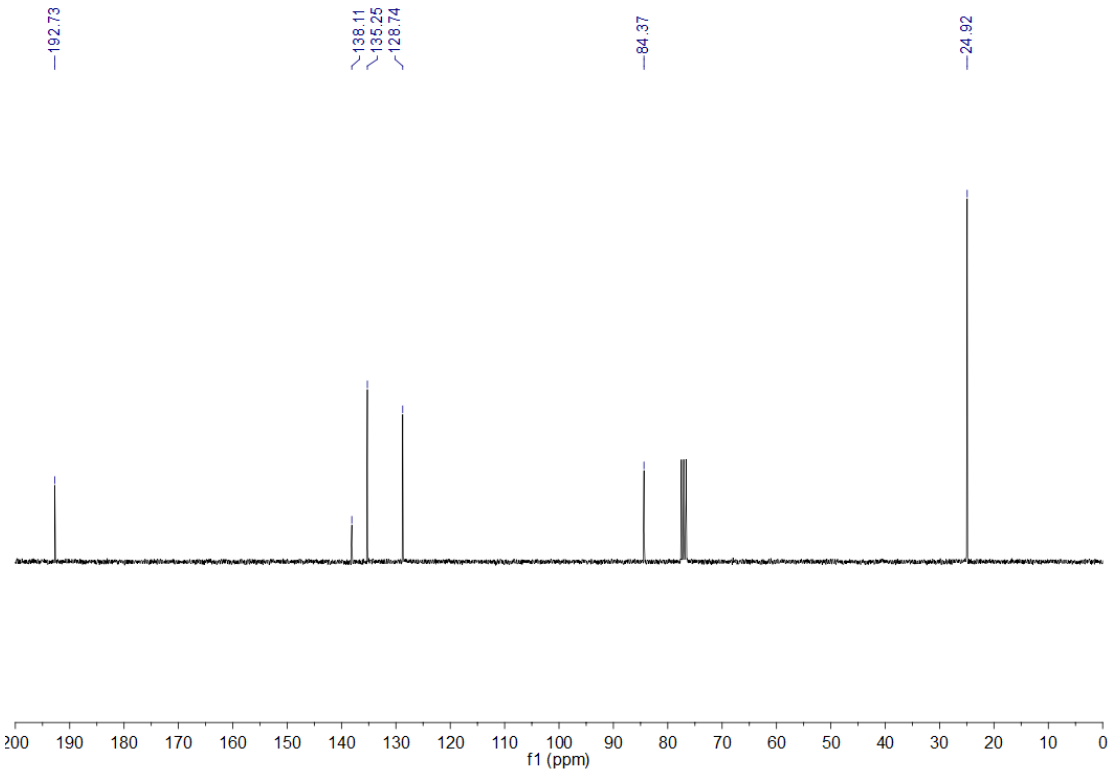
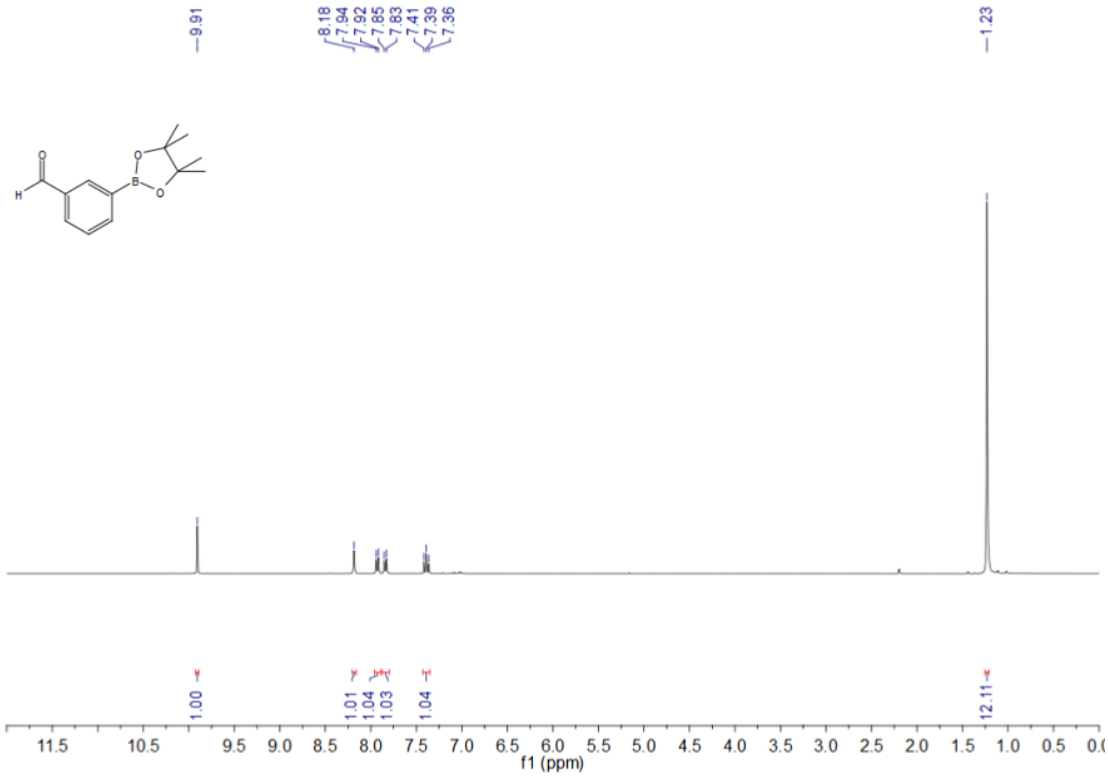
42.57
25.01
f1 (ppm)

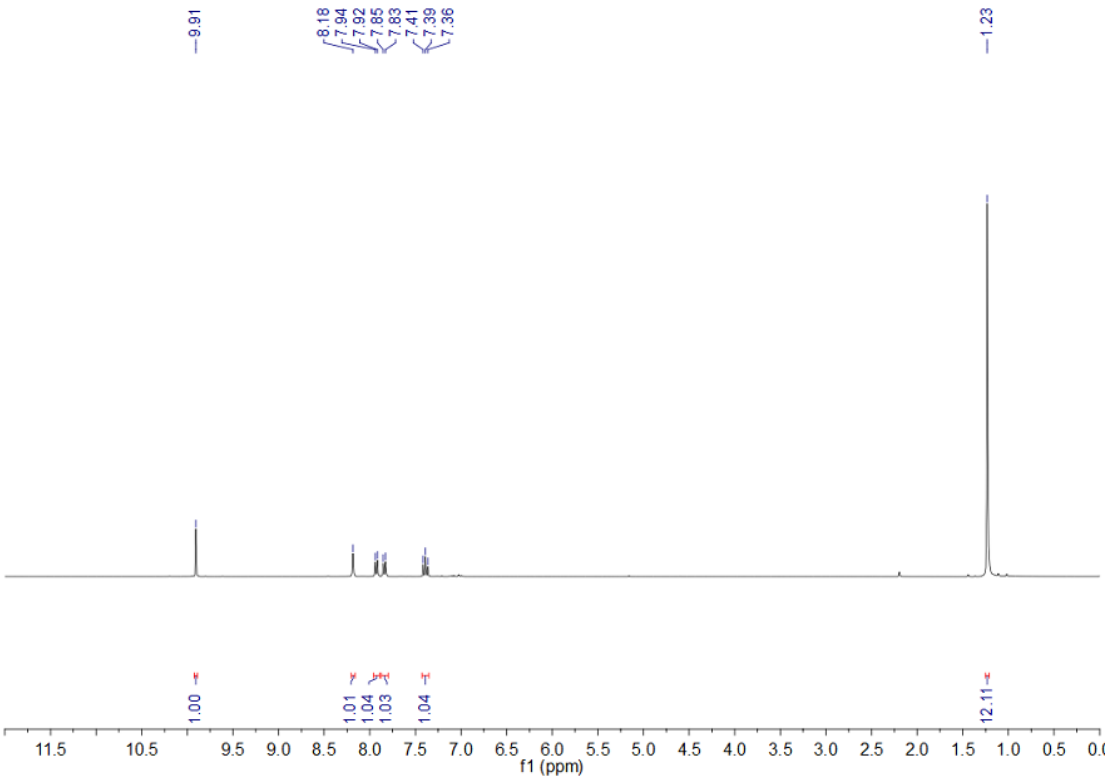
Entry 1 Table 4.1 Compound 4.1



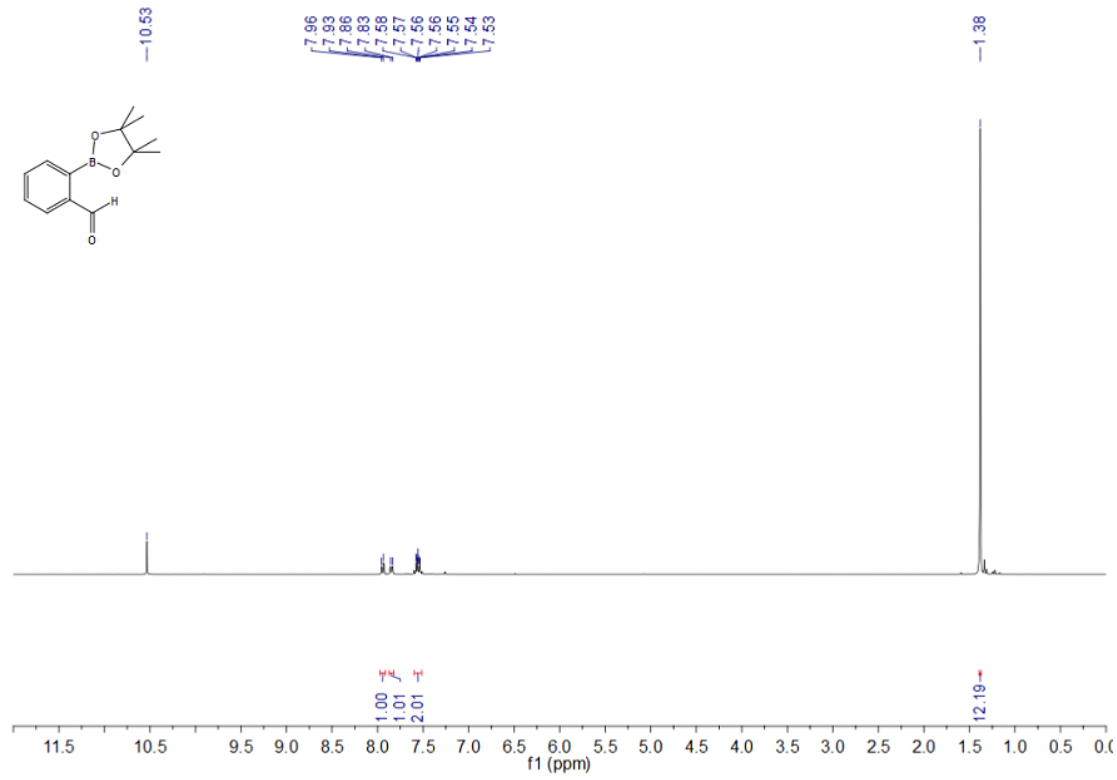


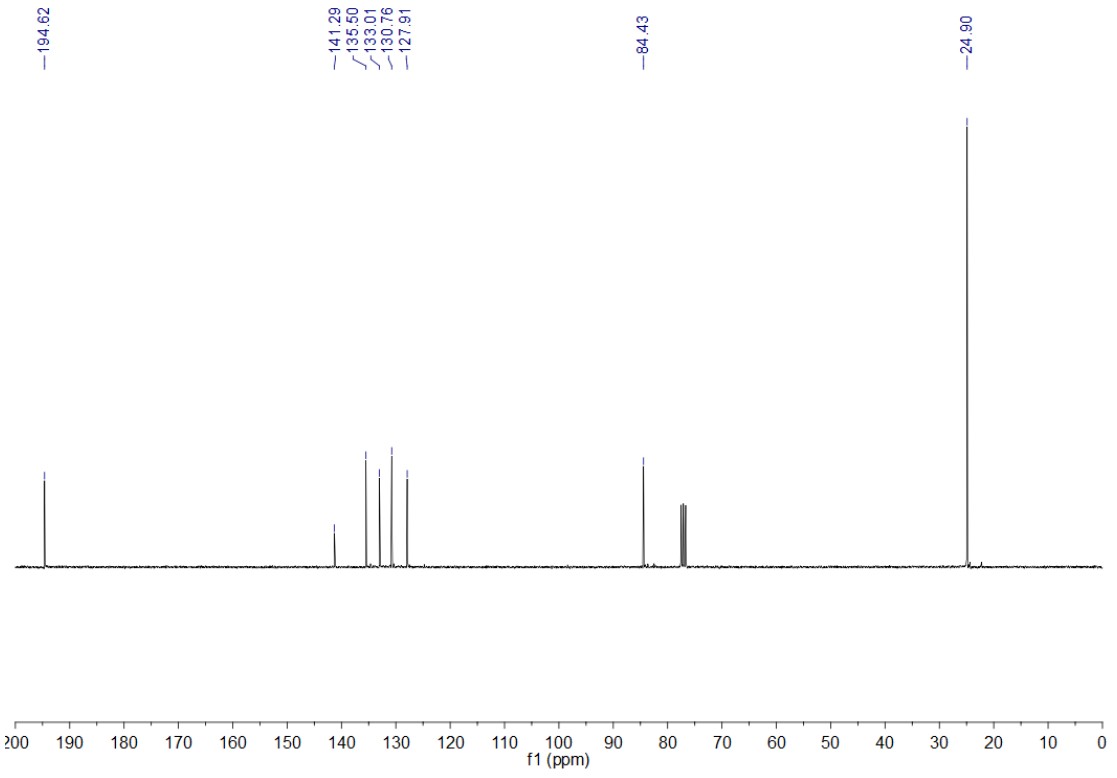
Entry 2 Table 4.1 Compound 4.2



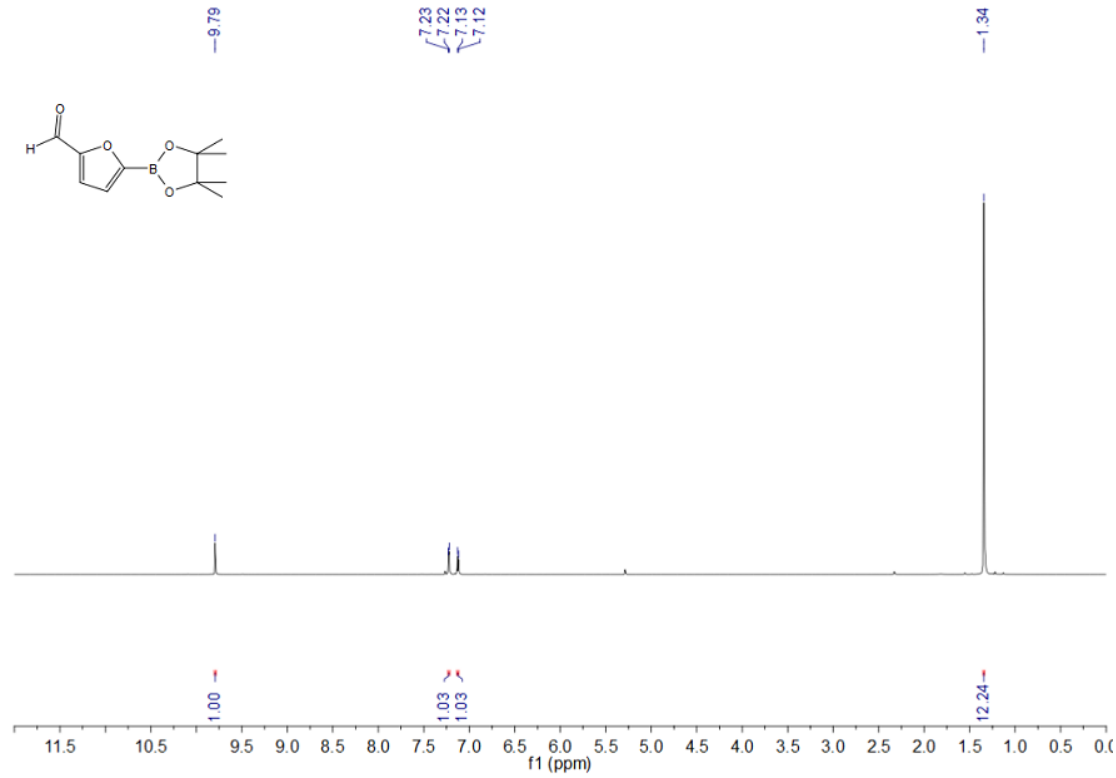


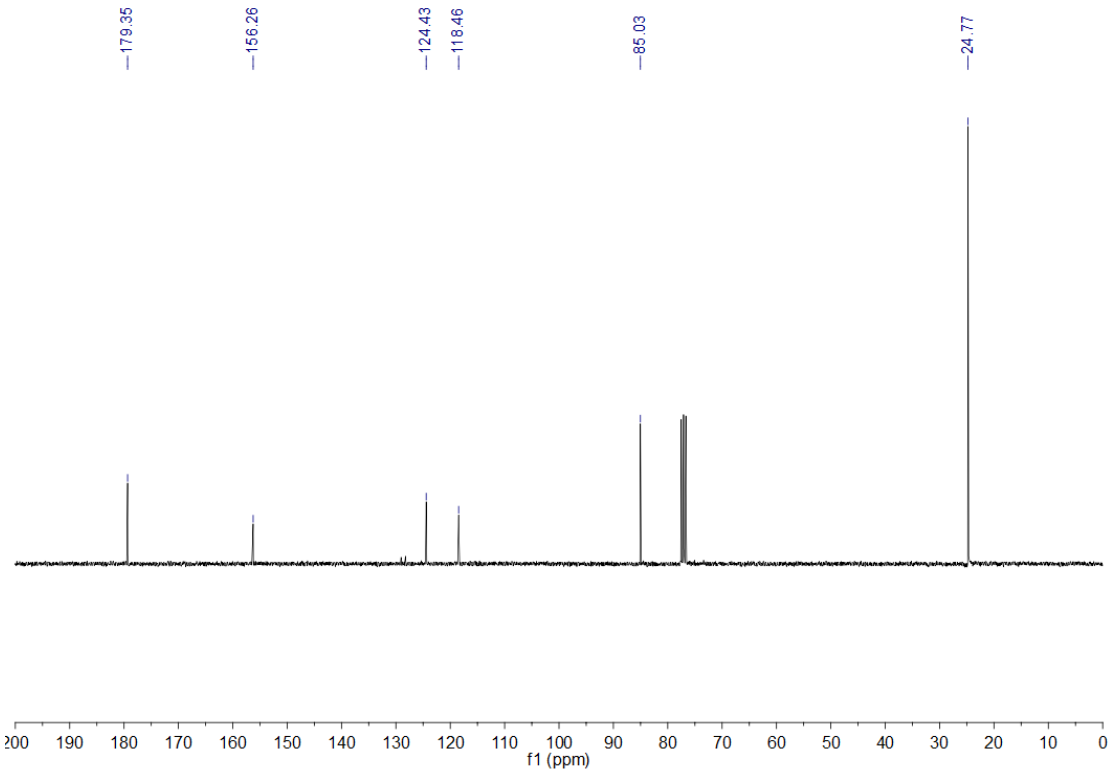
Entry 3 Table 4.1 Compound 4.3



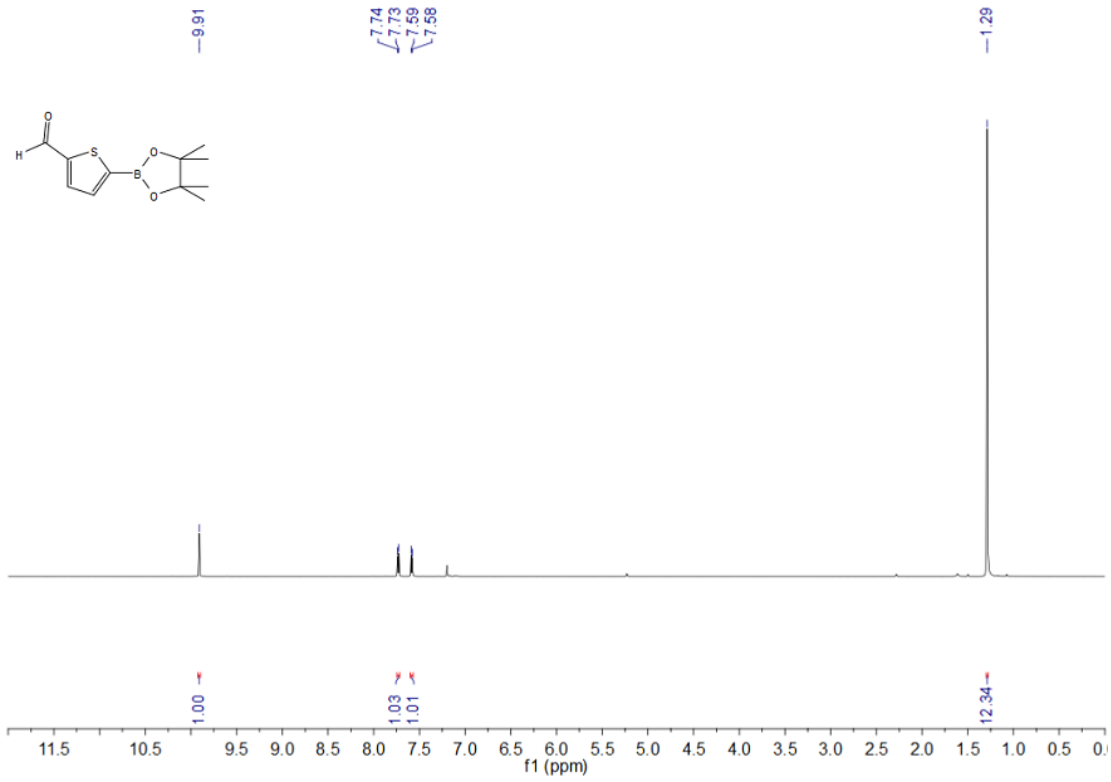


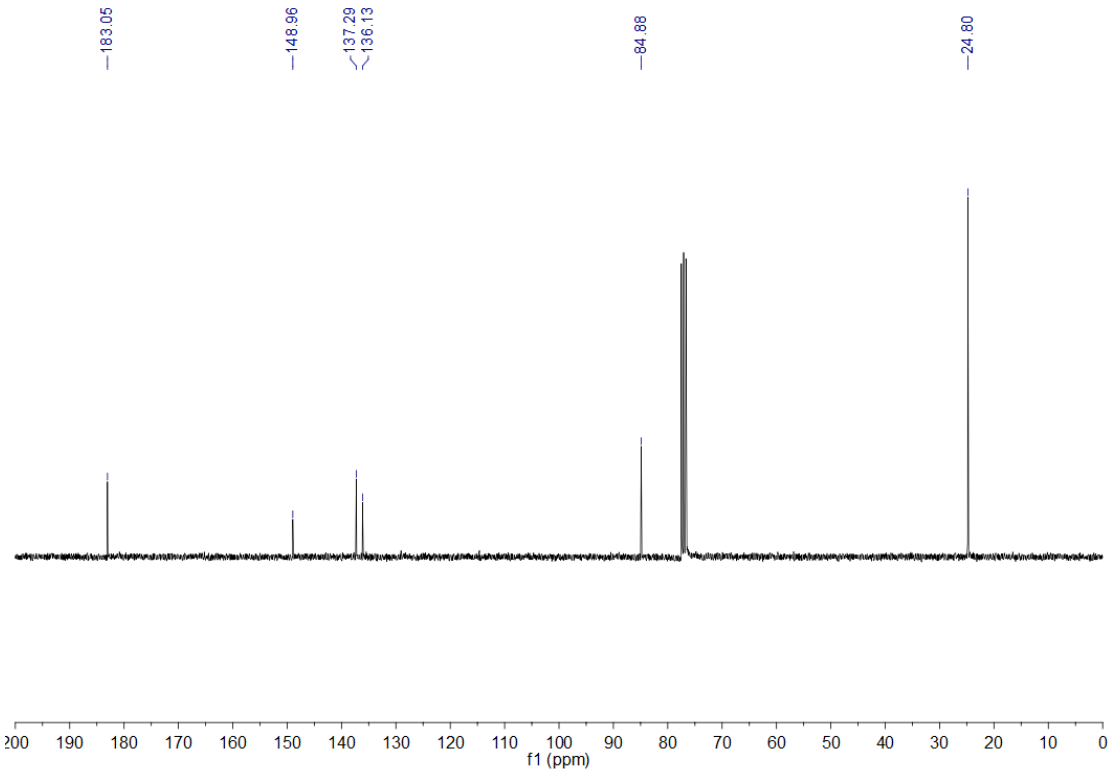
Entry 4 Table 4.1 Compound 4.4



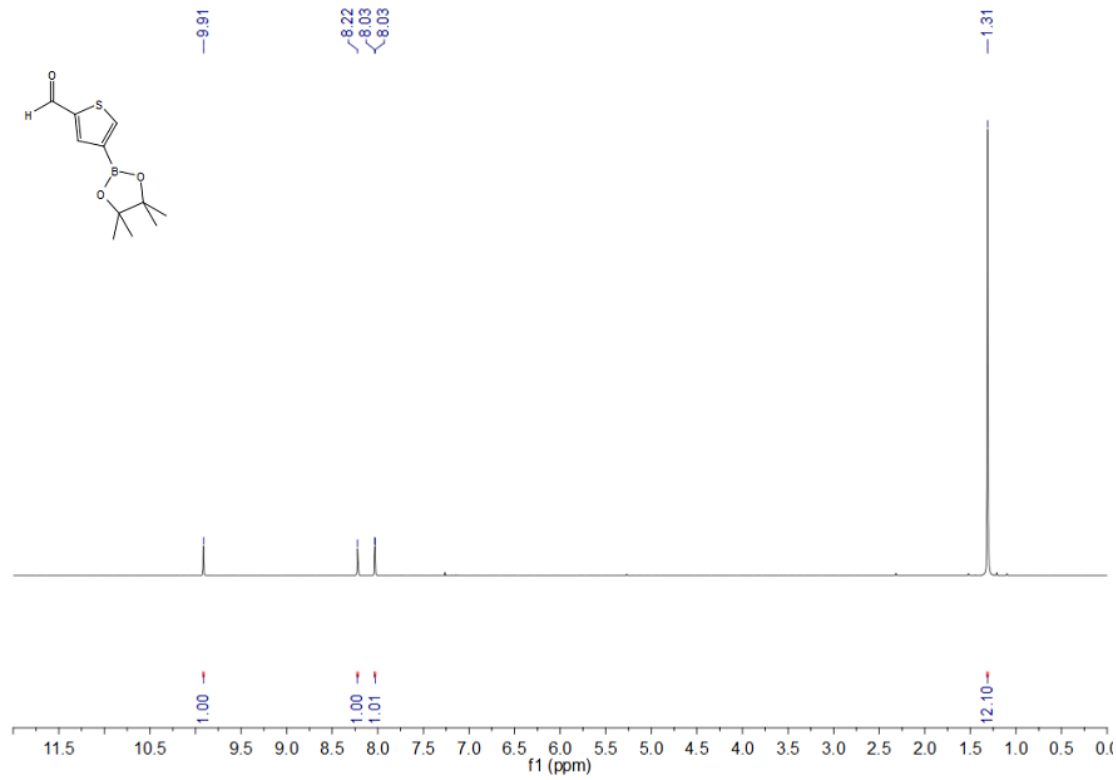


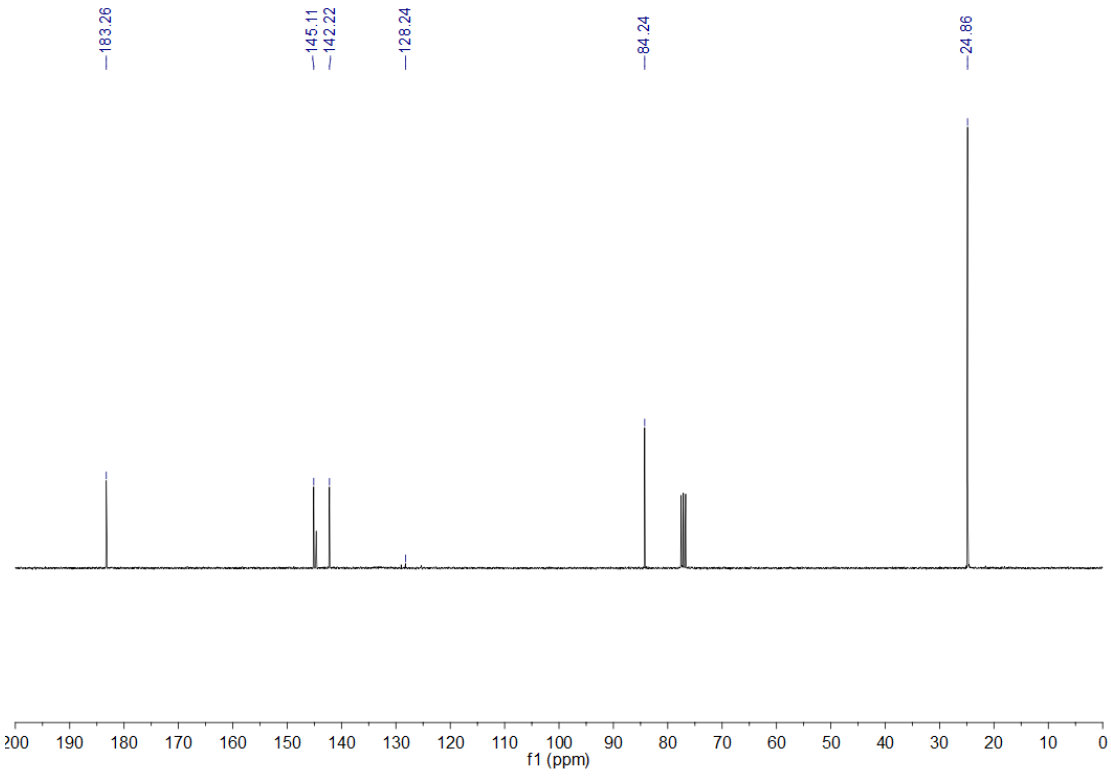
Entry 5 Table 4.1 Compound 4.5



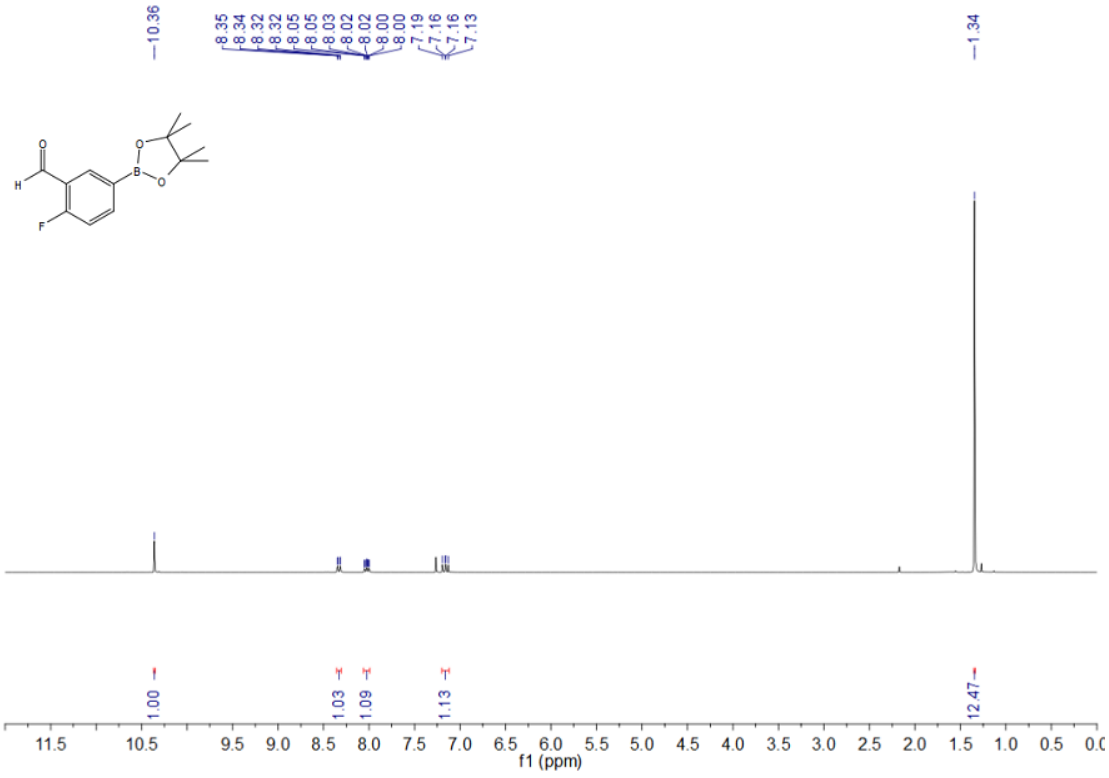


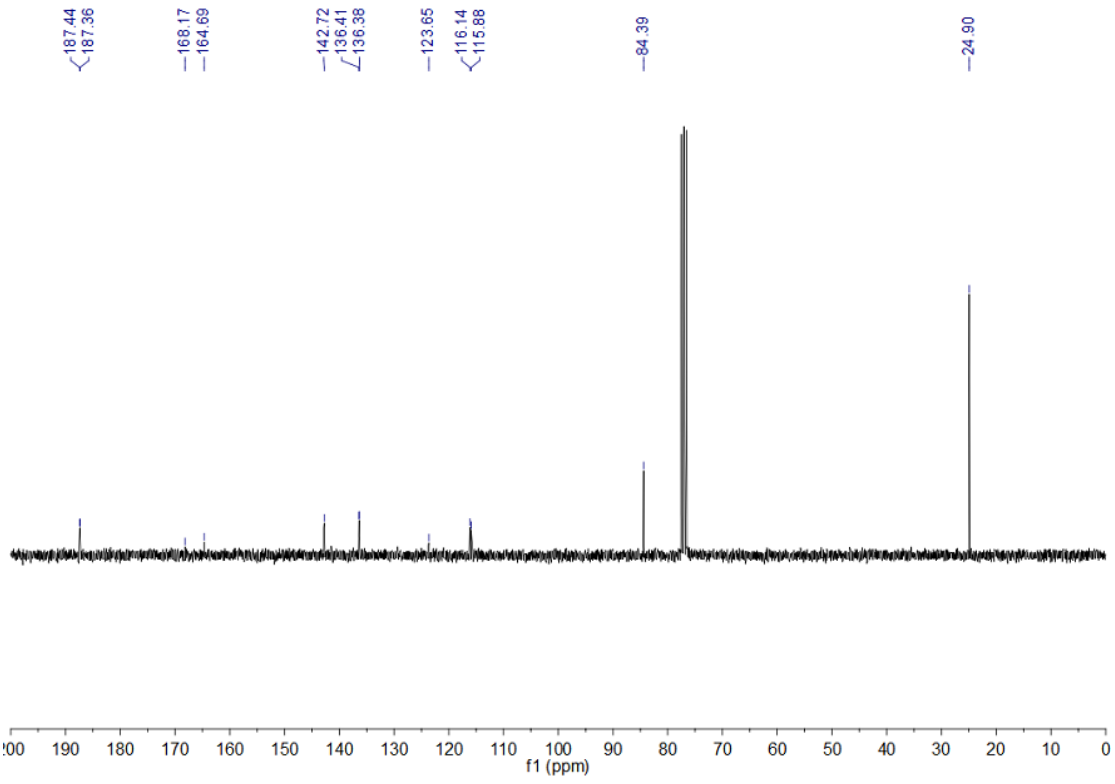
Entry 6 Table 4.1 Compound 4.6



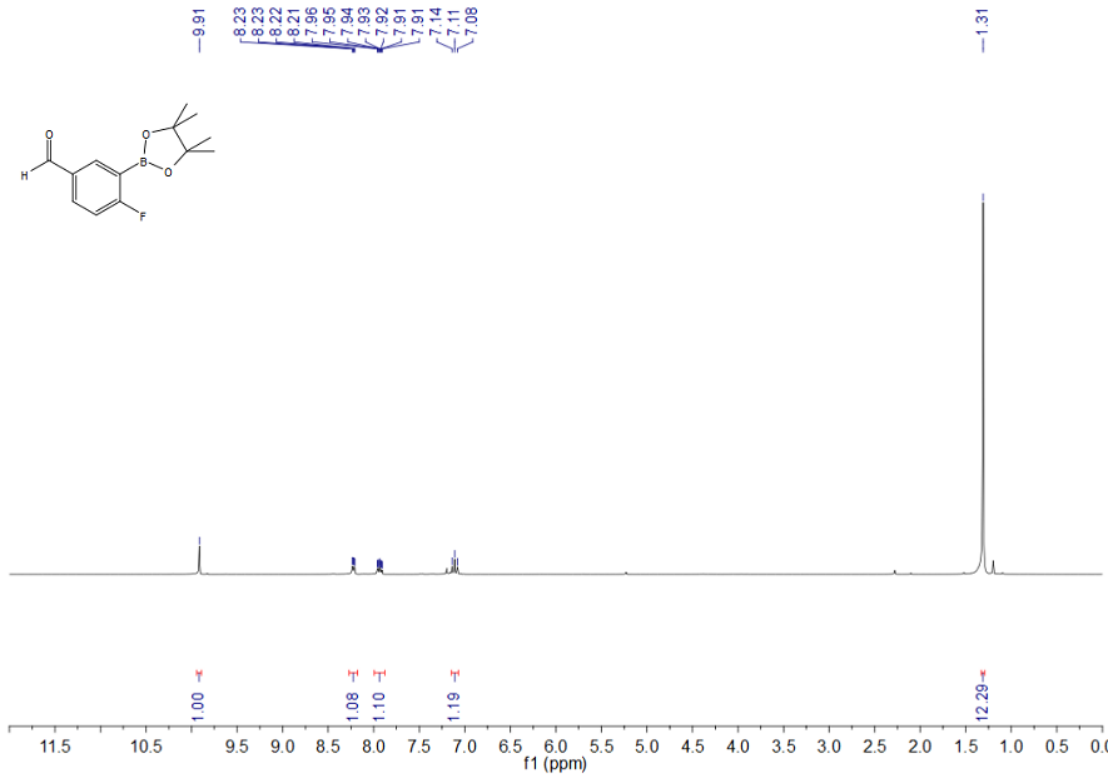


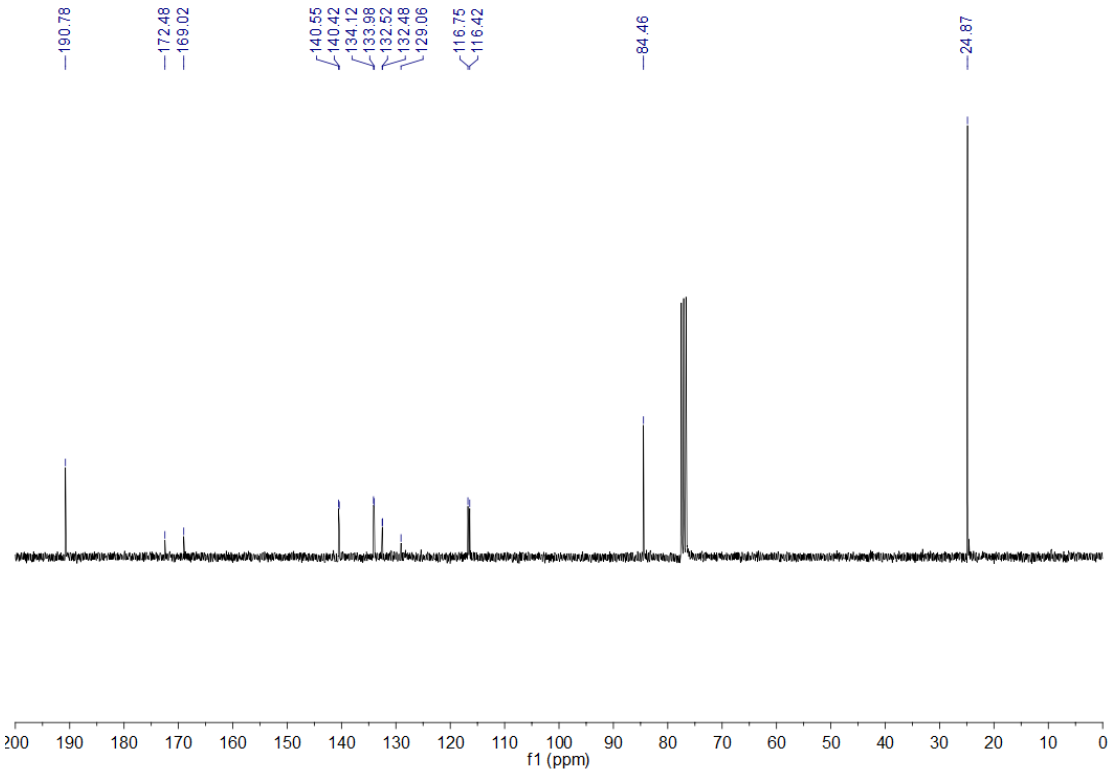
Entry 7 Table 4.1 Compound 4.7



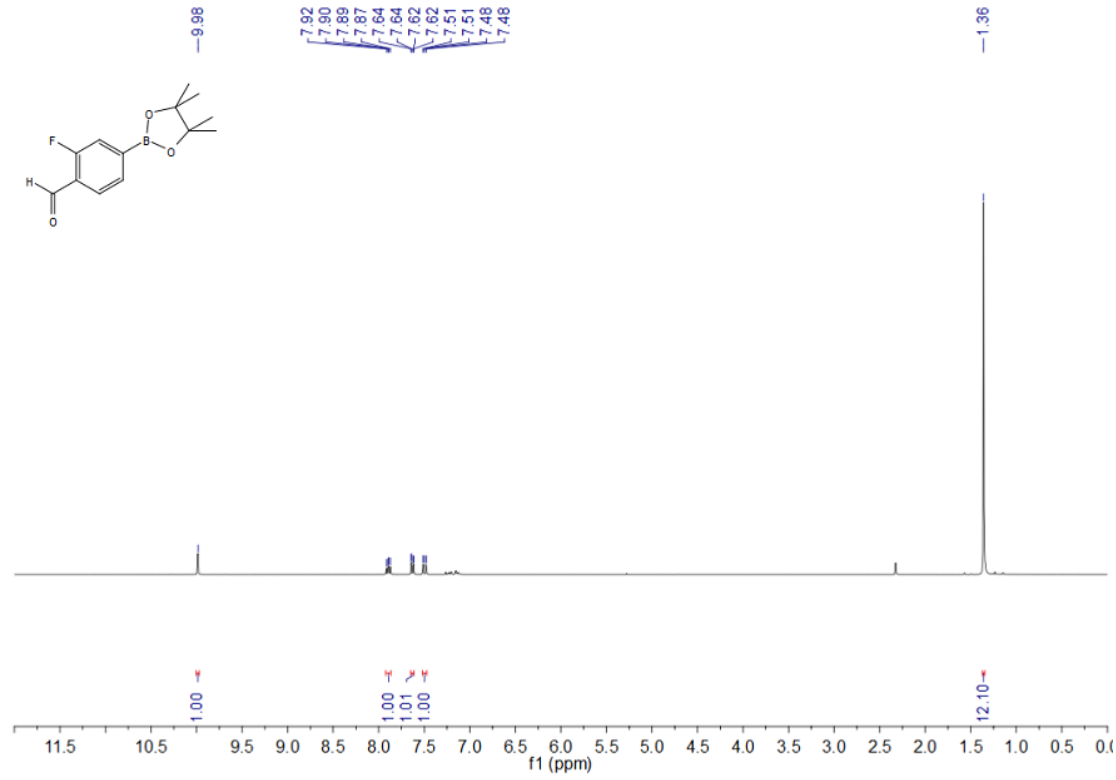


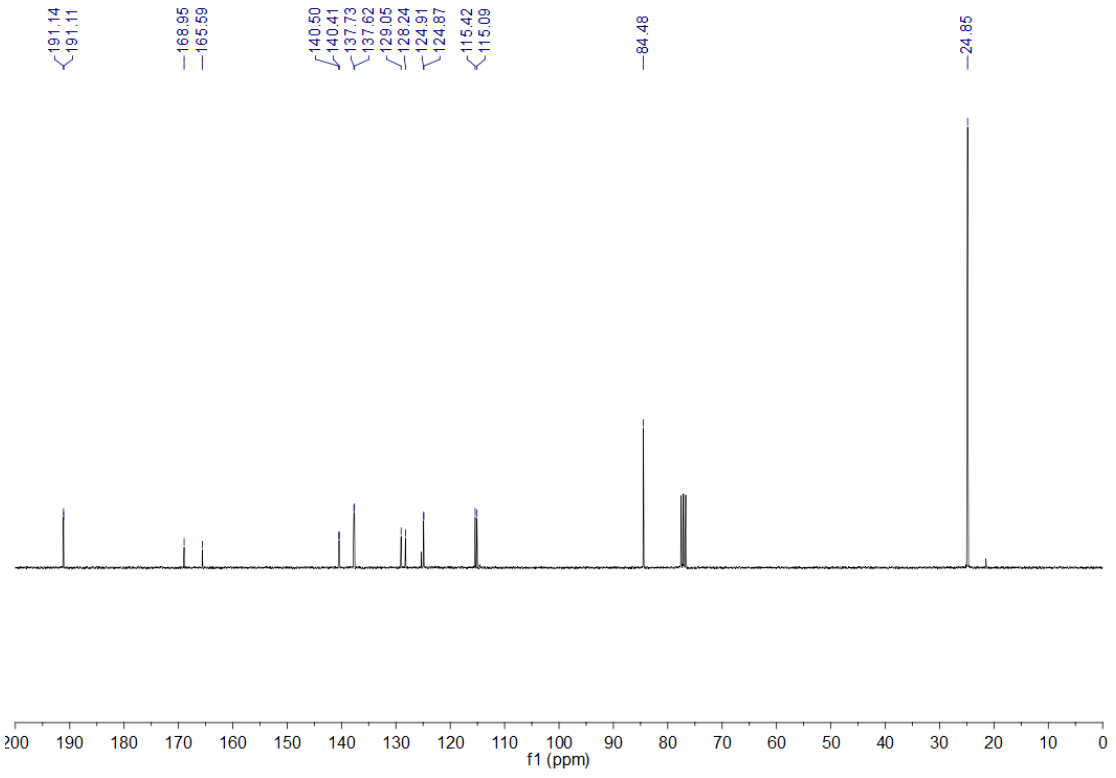
Entry 8 Table 4.1 Compound 4.8



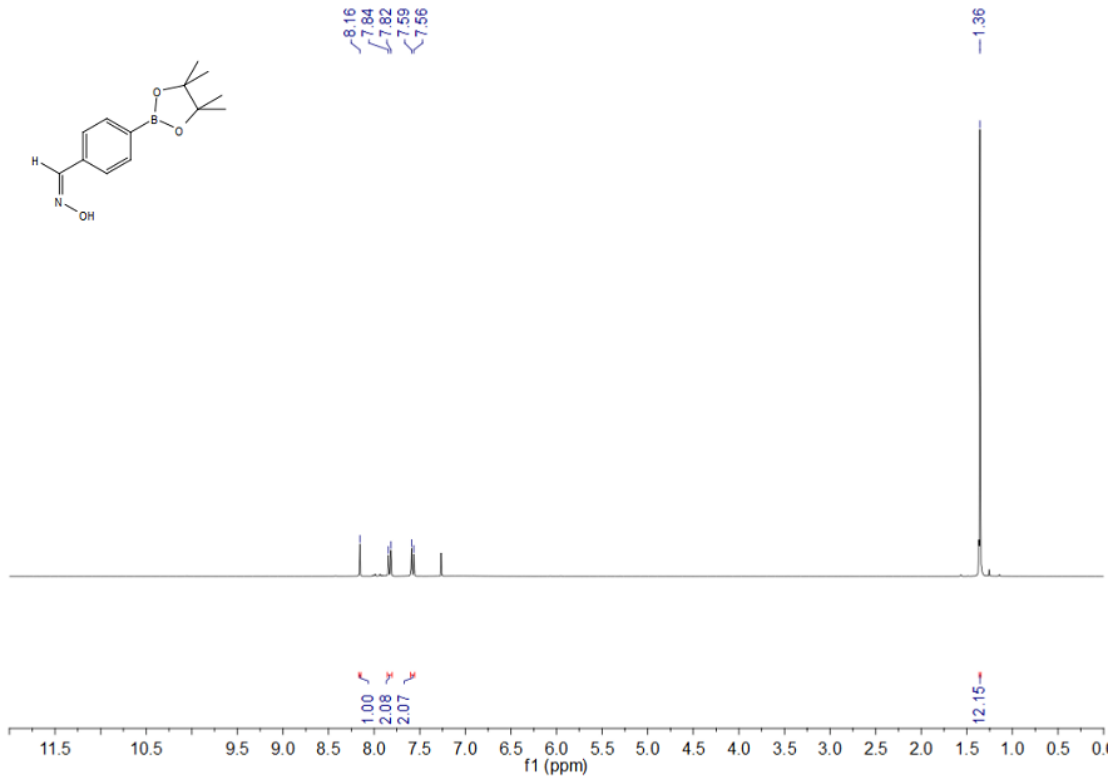


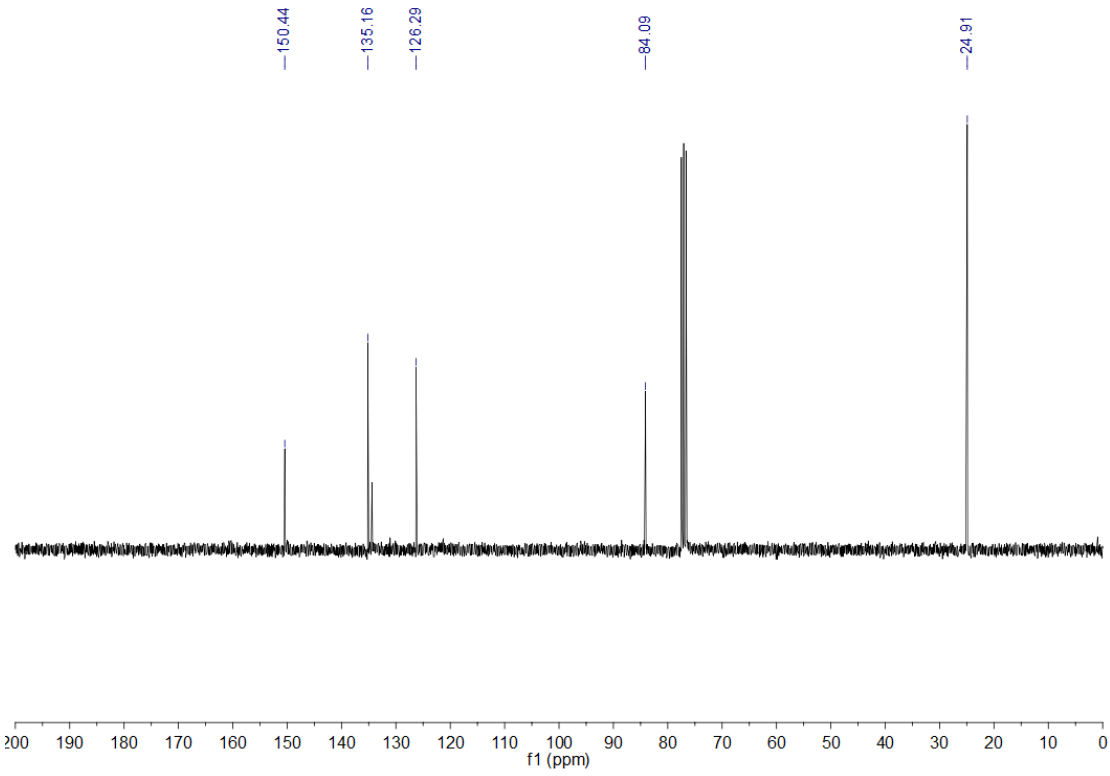
Entry 9 Table 4.1 Compound 4.9



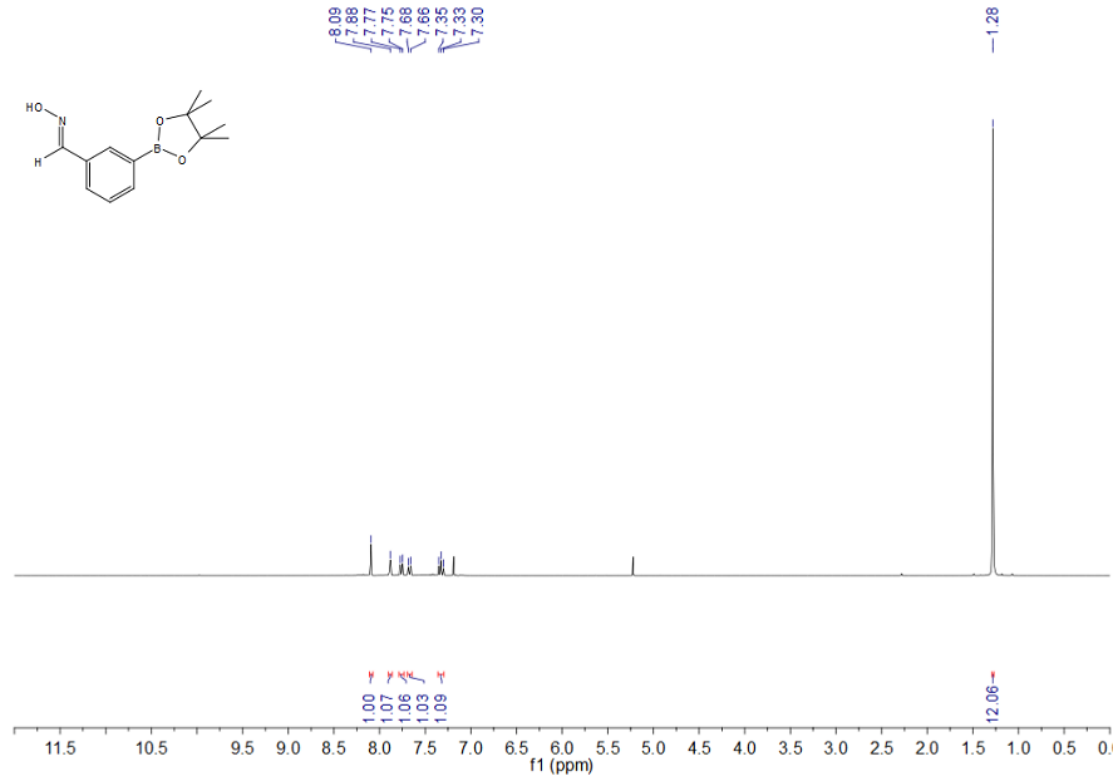


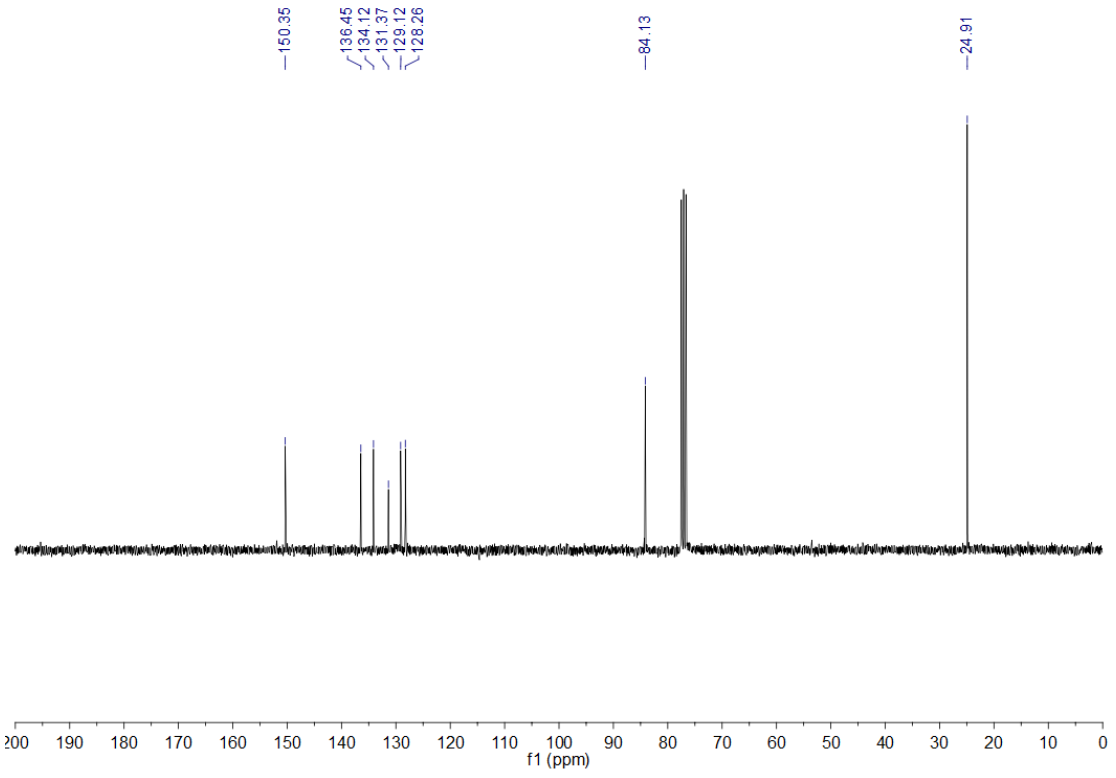
Entry 1 Table 4.2 Compound 4.10





Entry 2 Table 4.2 Compound 4.11





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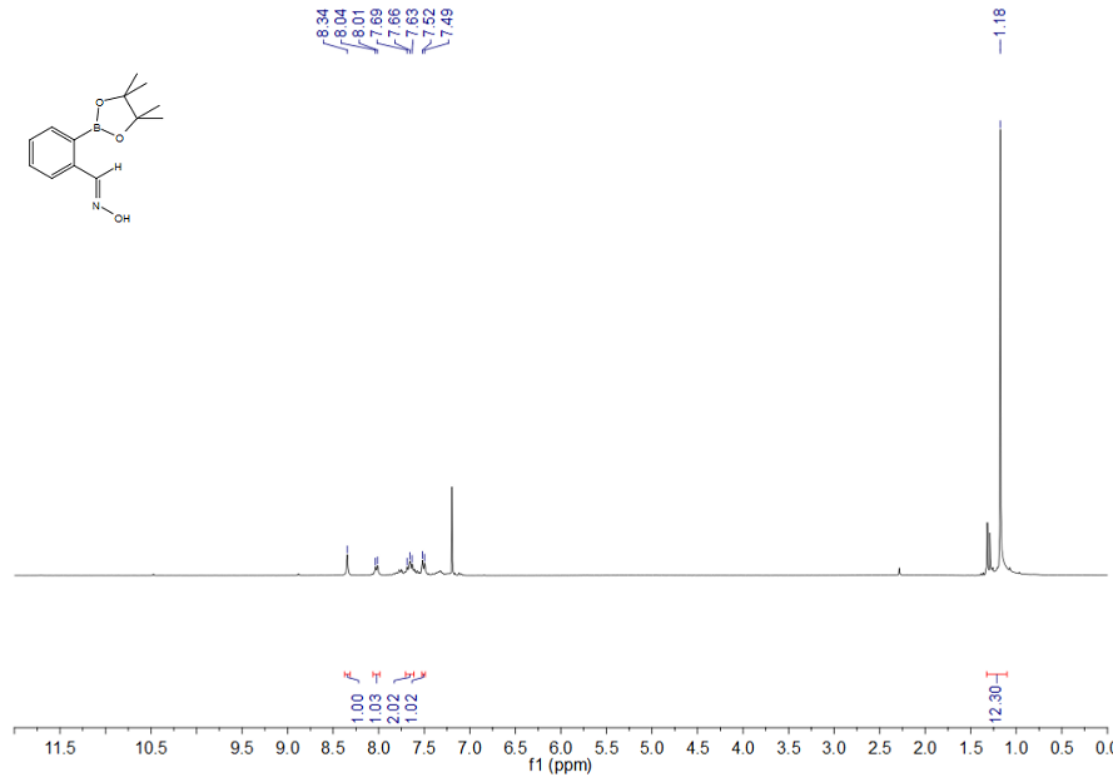
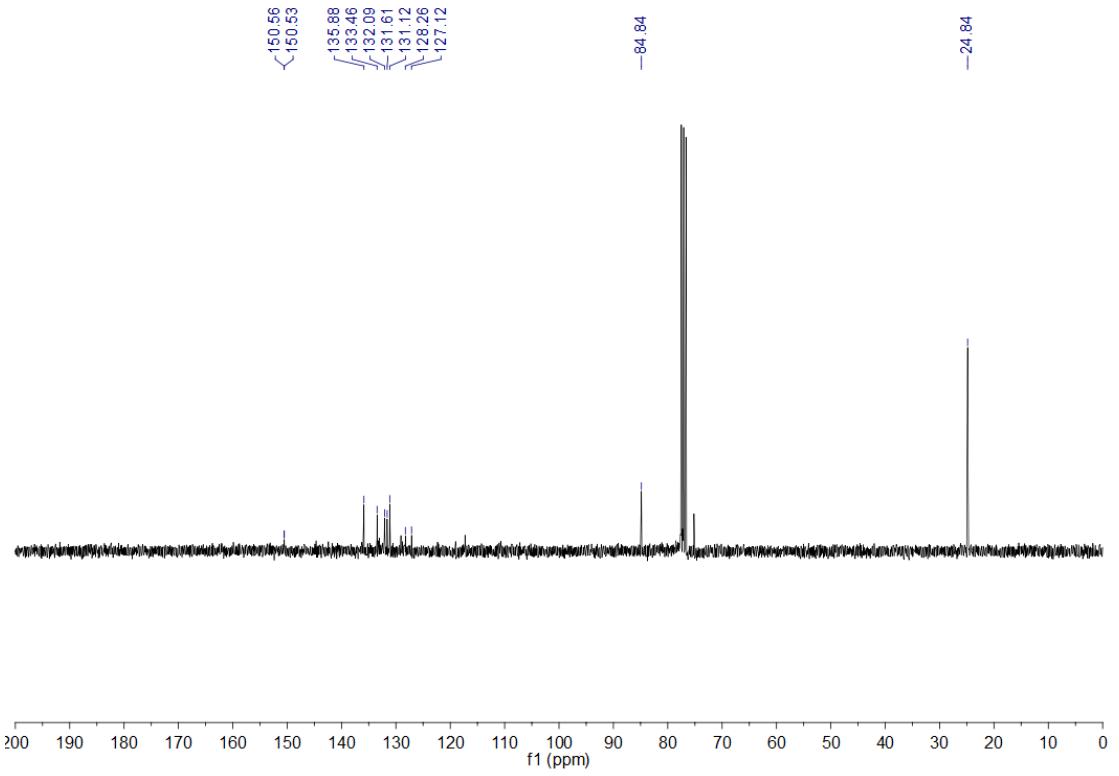
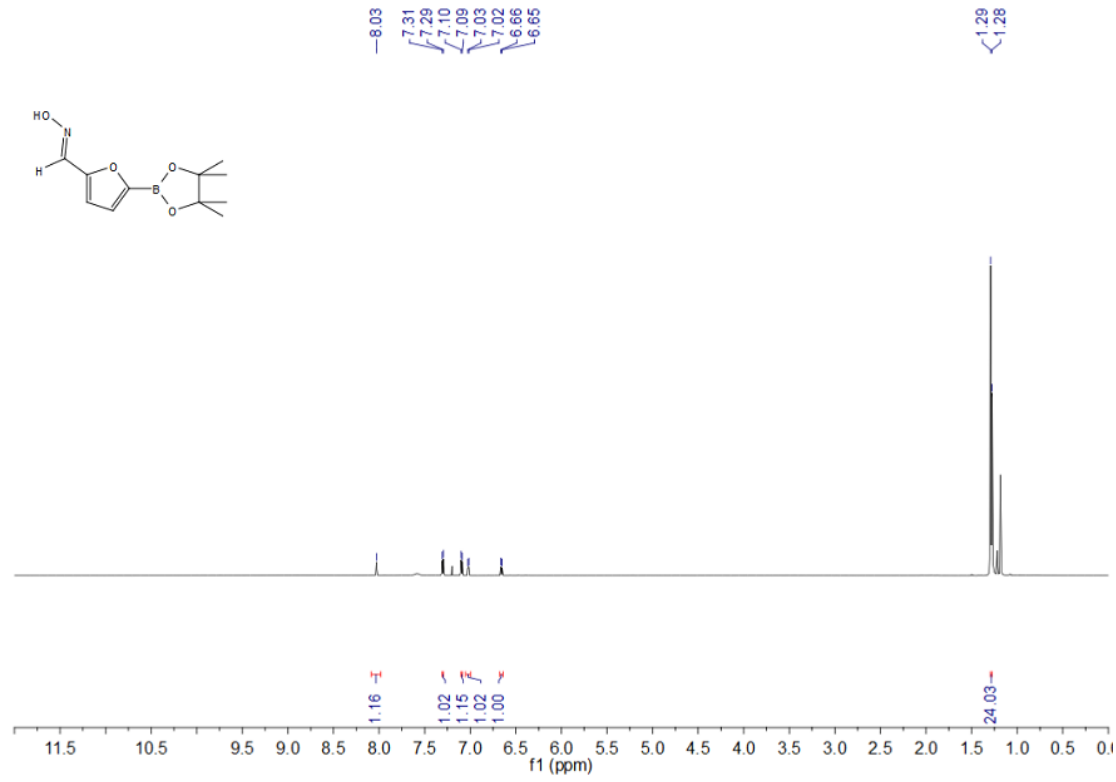
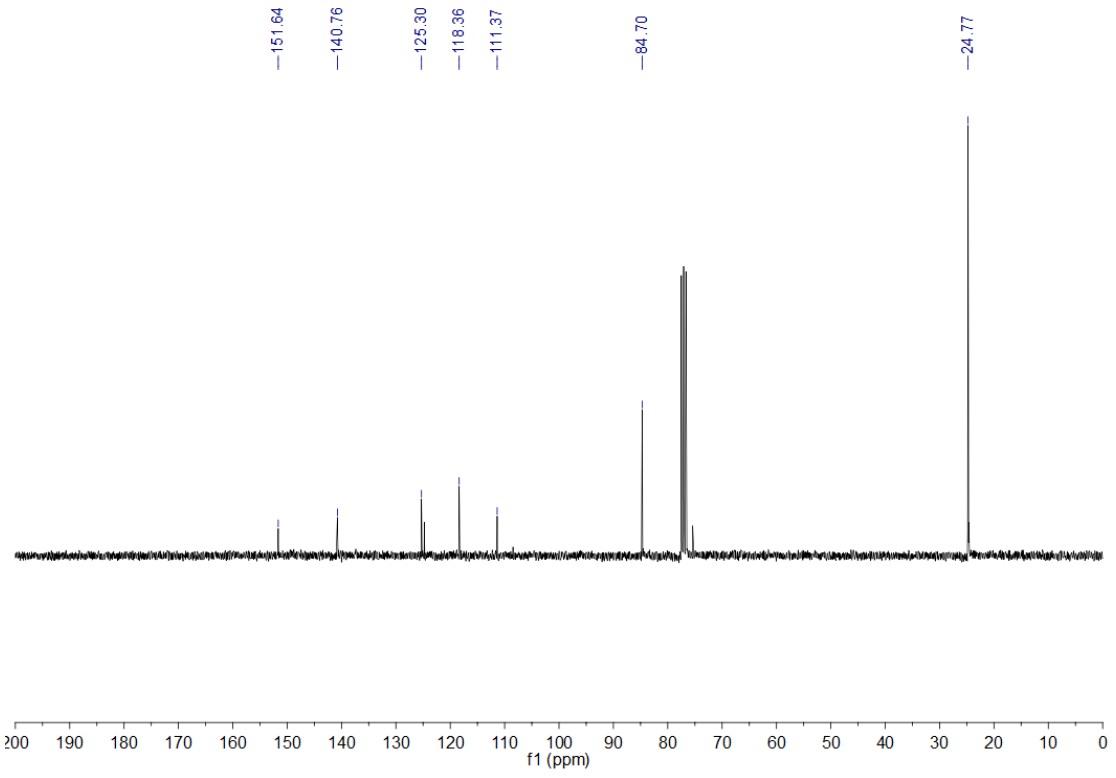


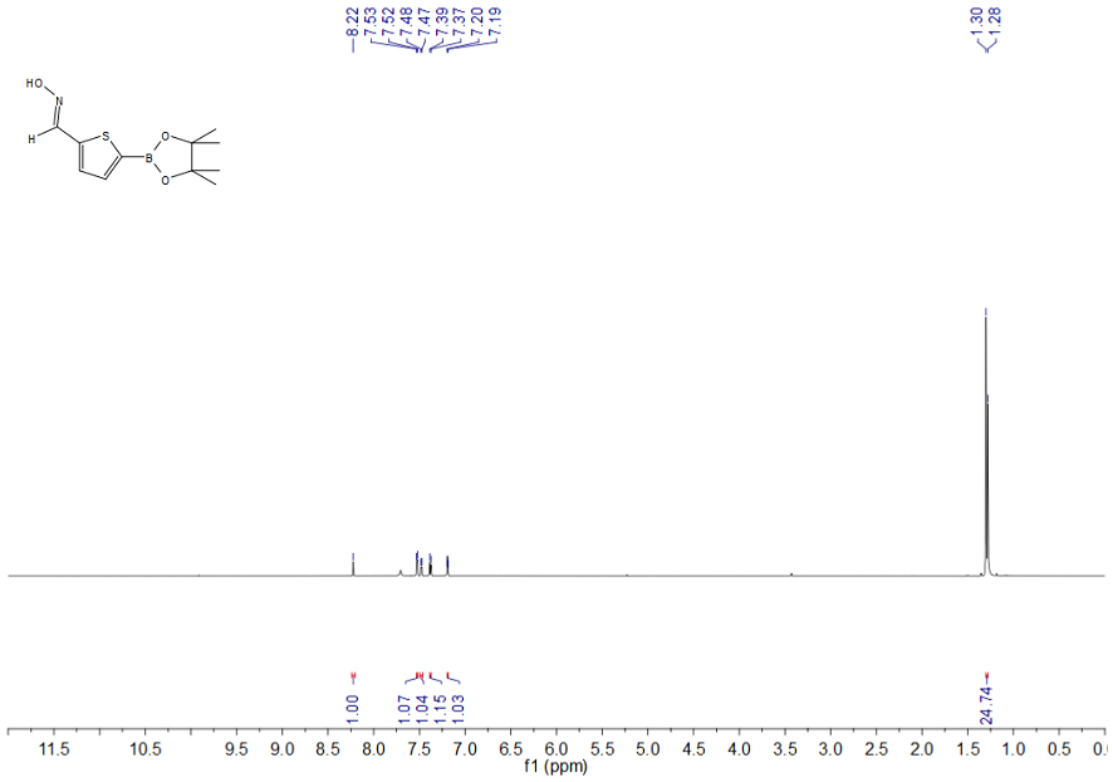


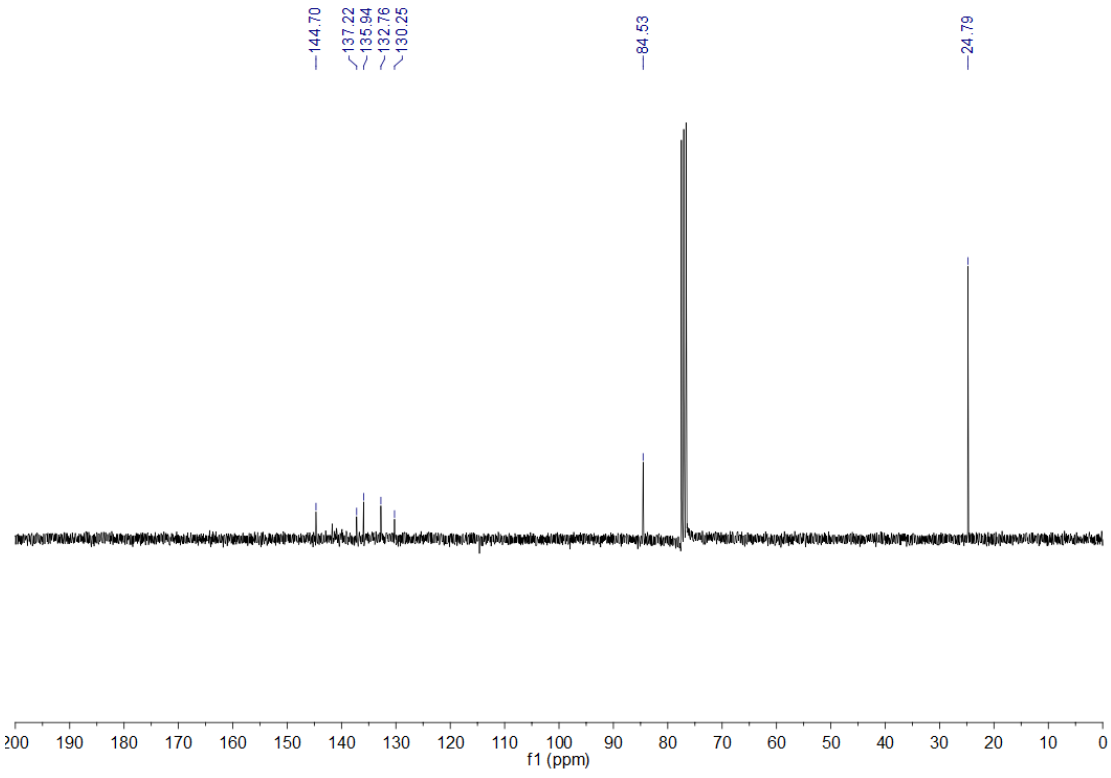
Entry 4 Table 4.2 Compound 4.13



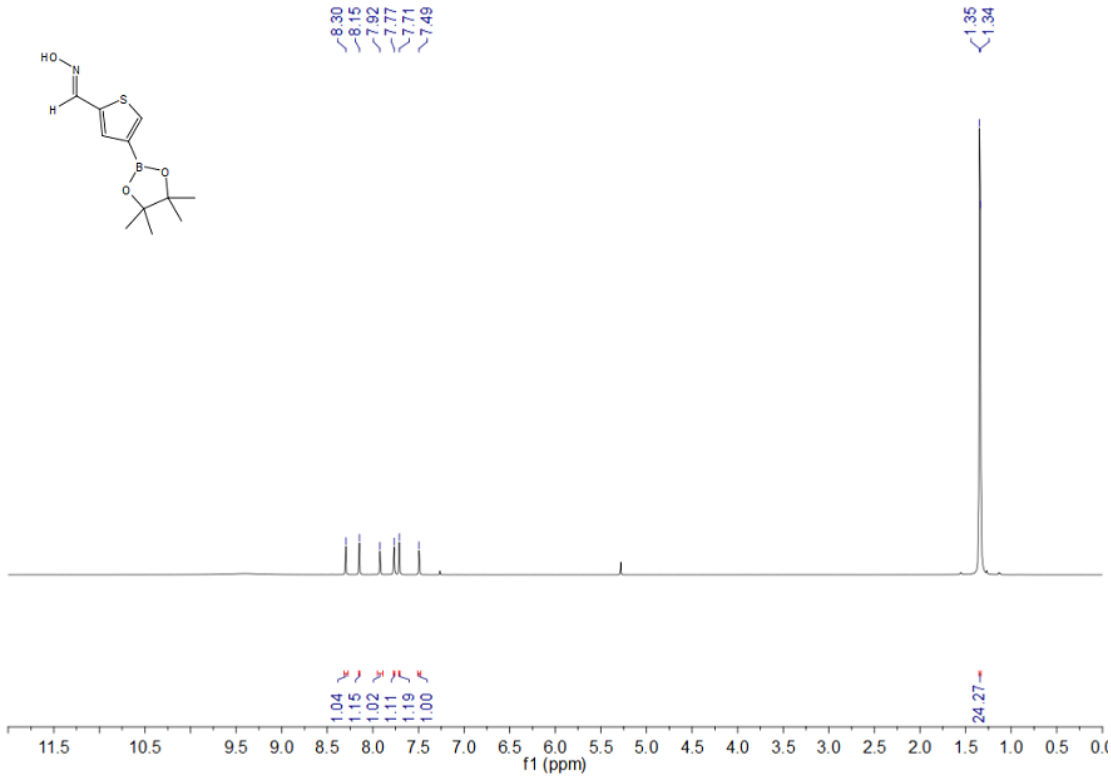


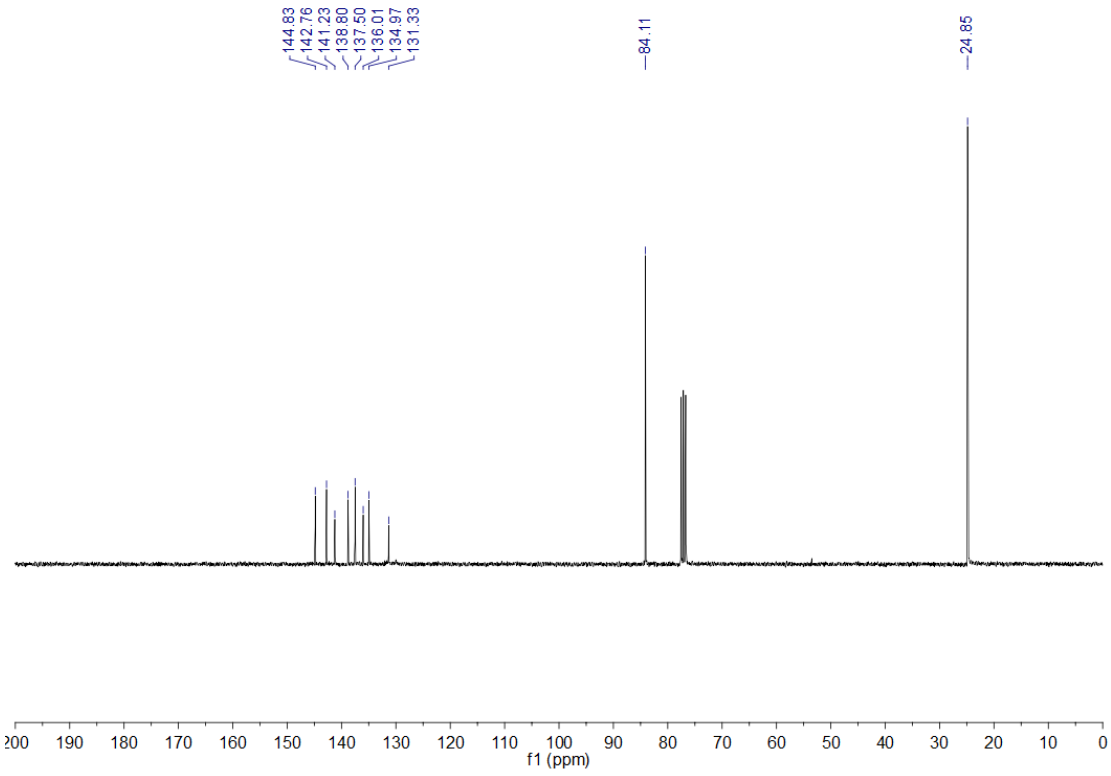
Entry 5 Table 4.2 Compound 4.14



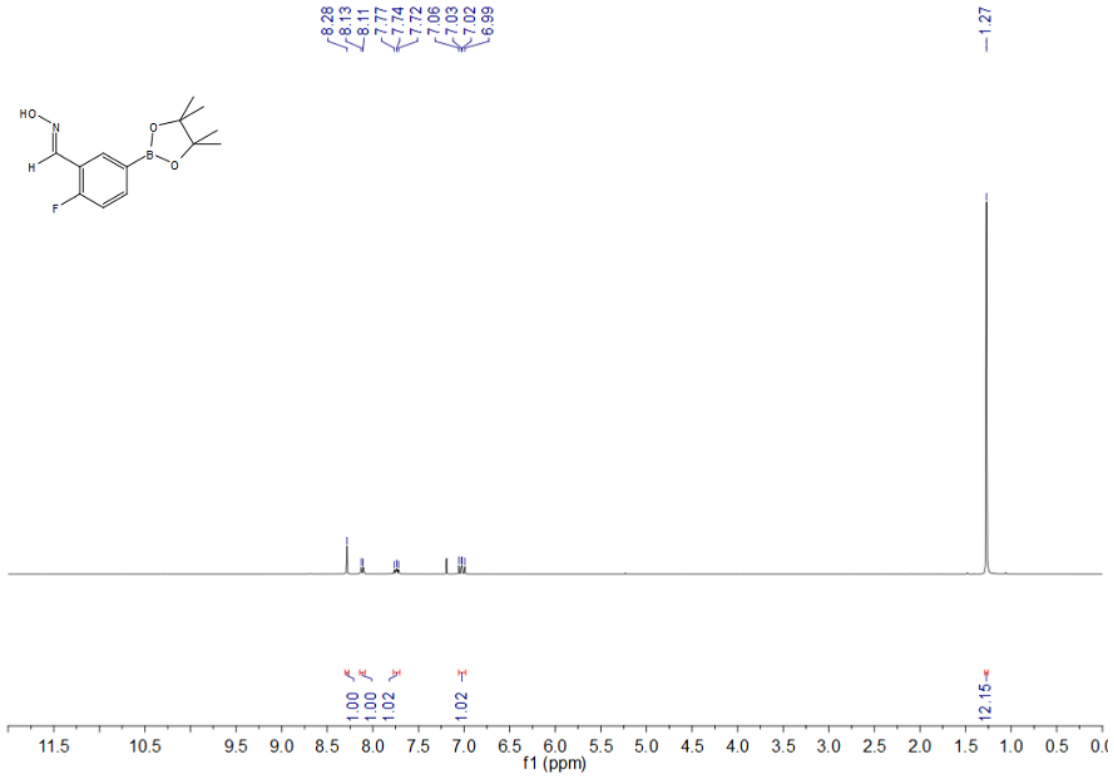


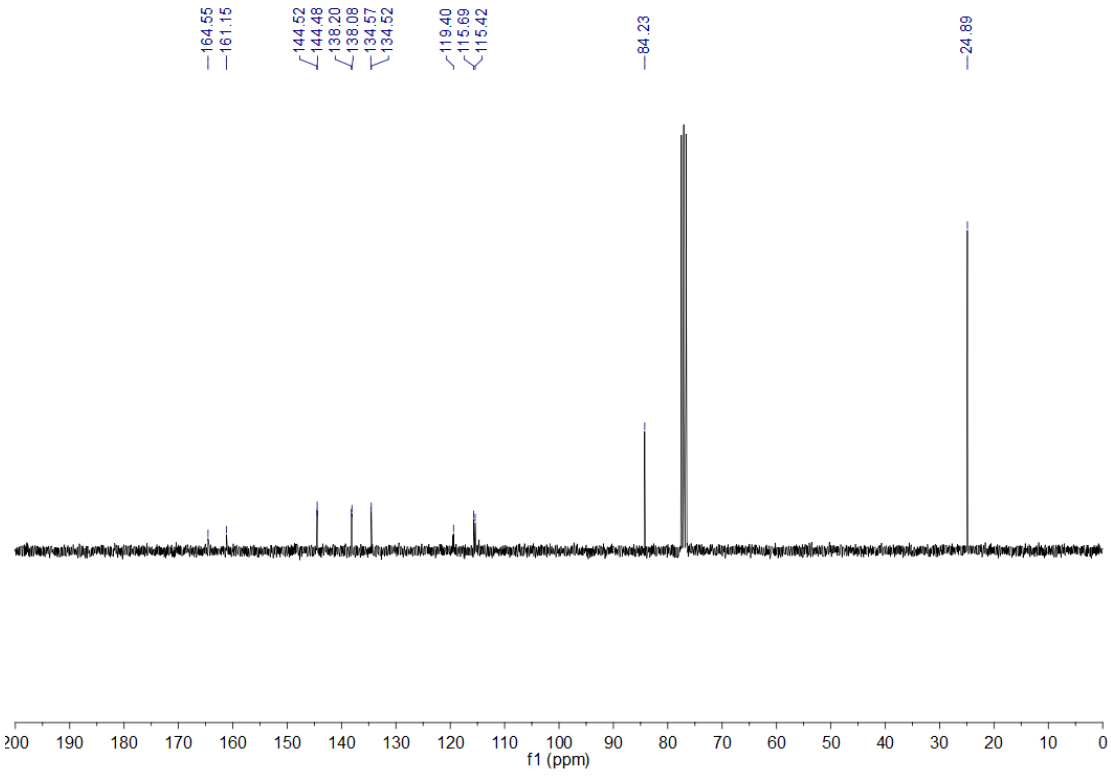
Entry 6 Table 4.2 Compound 4.15



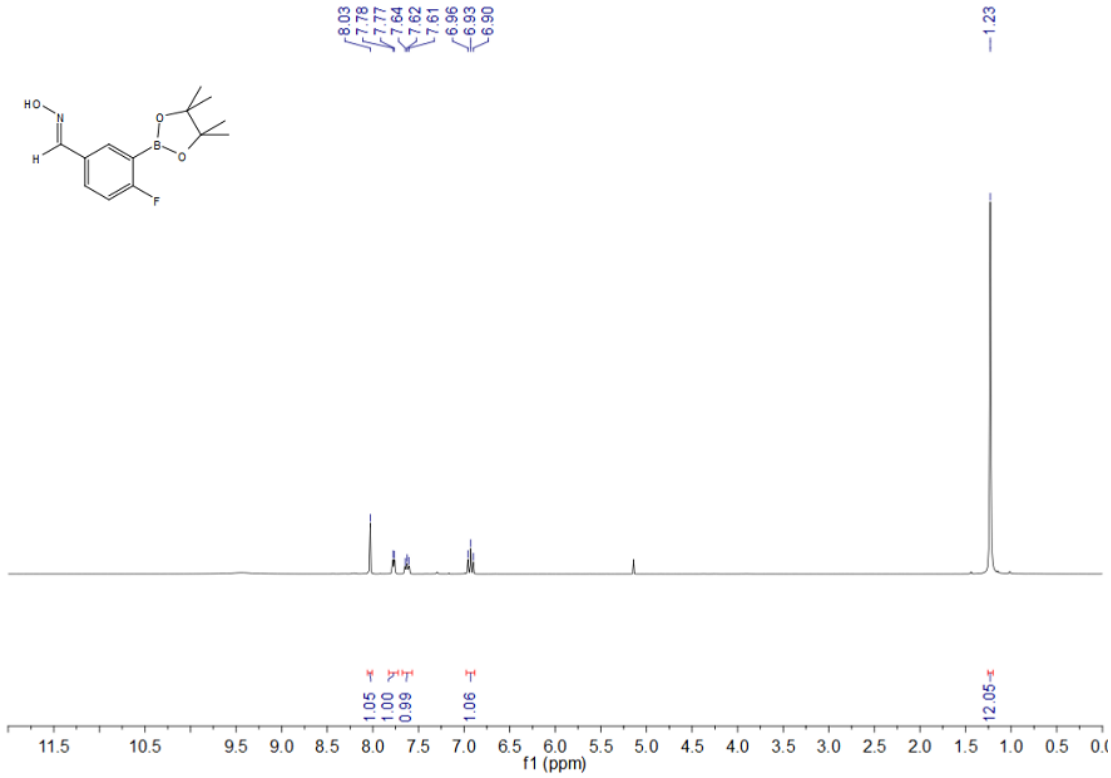


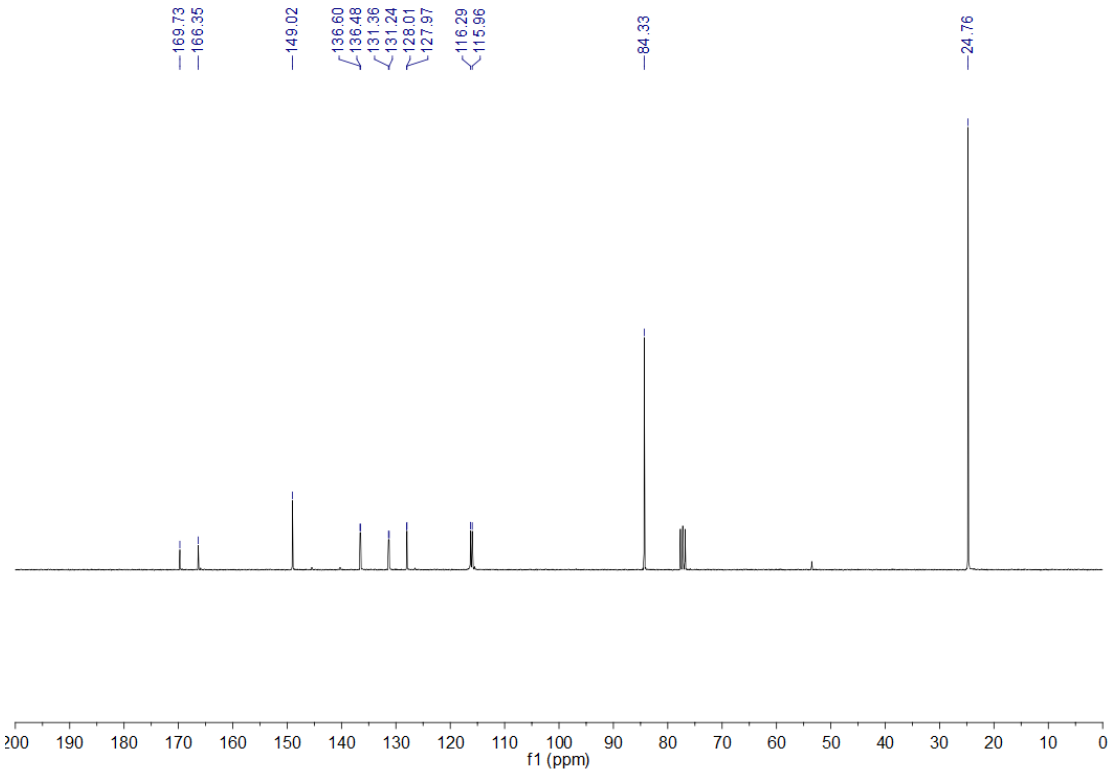
Entry 7 Table 4.2 Compound 4.16





Entry 8 Table 4.2 Compound 4.17





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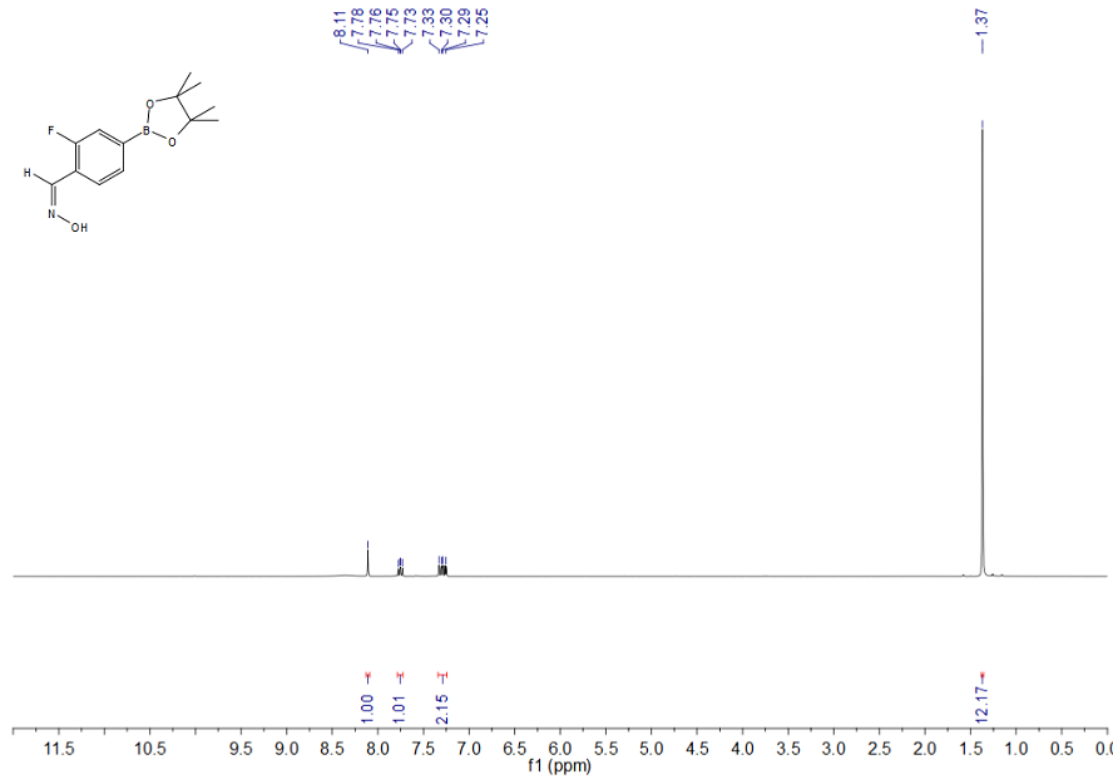

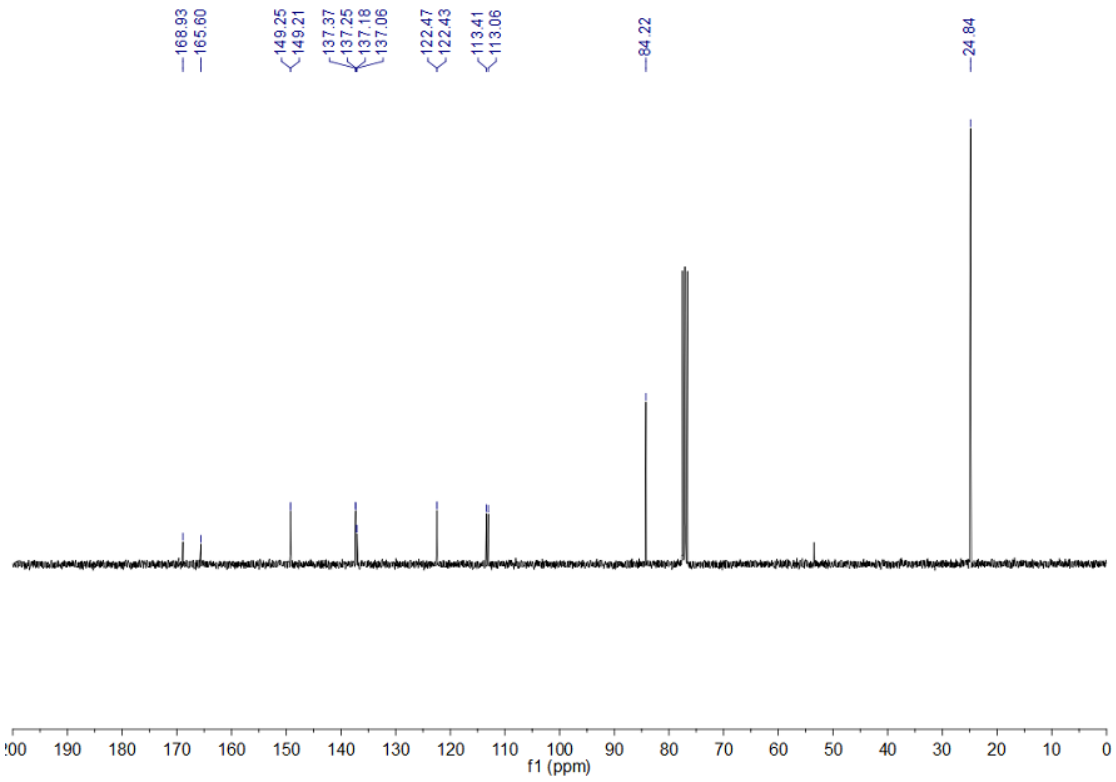

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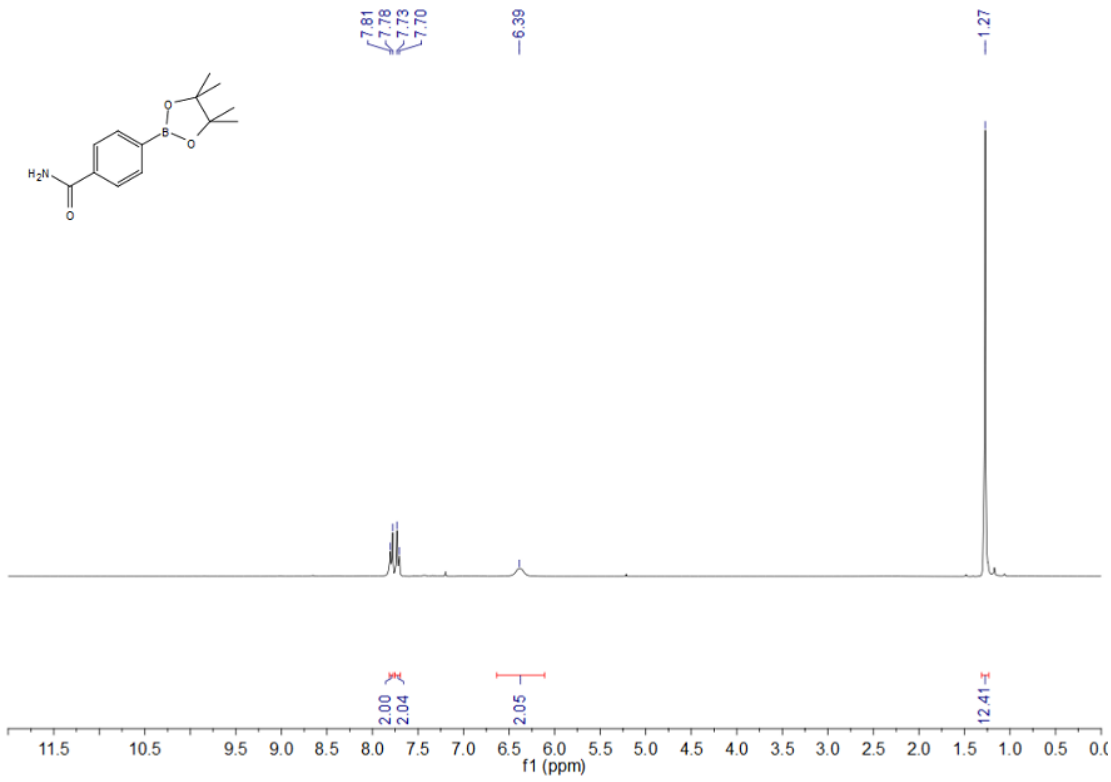
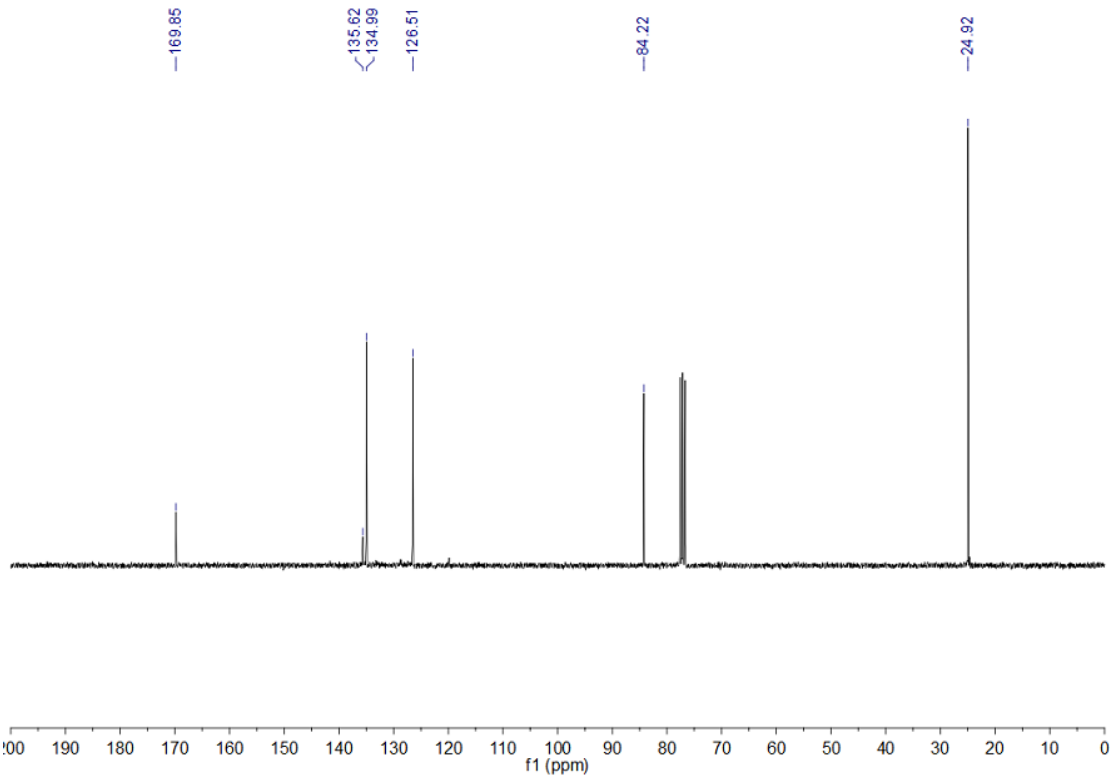
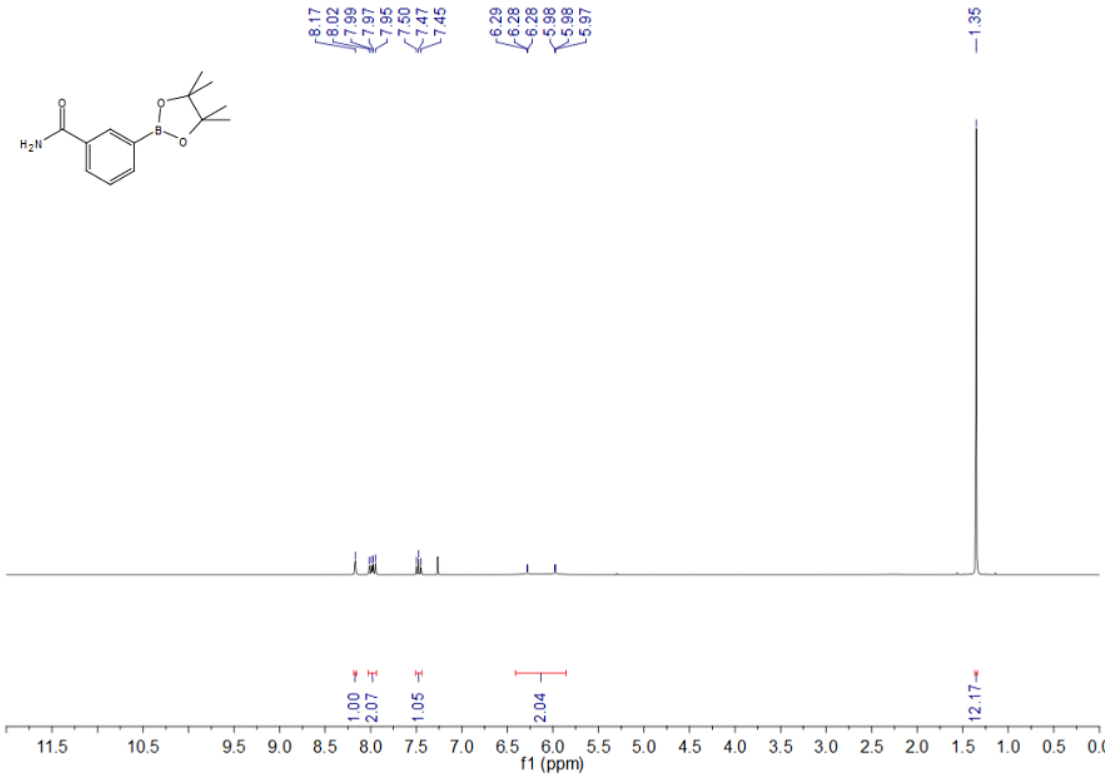
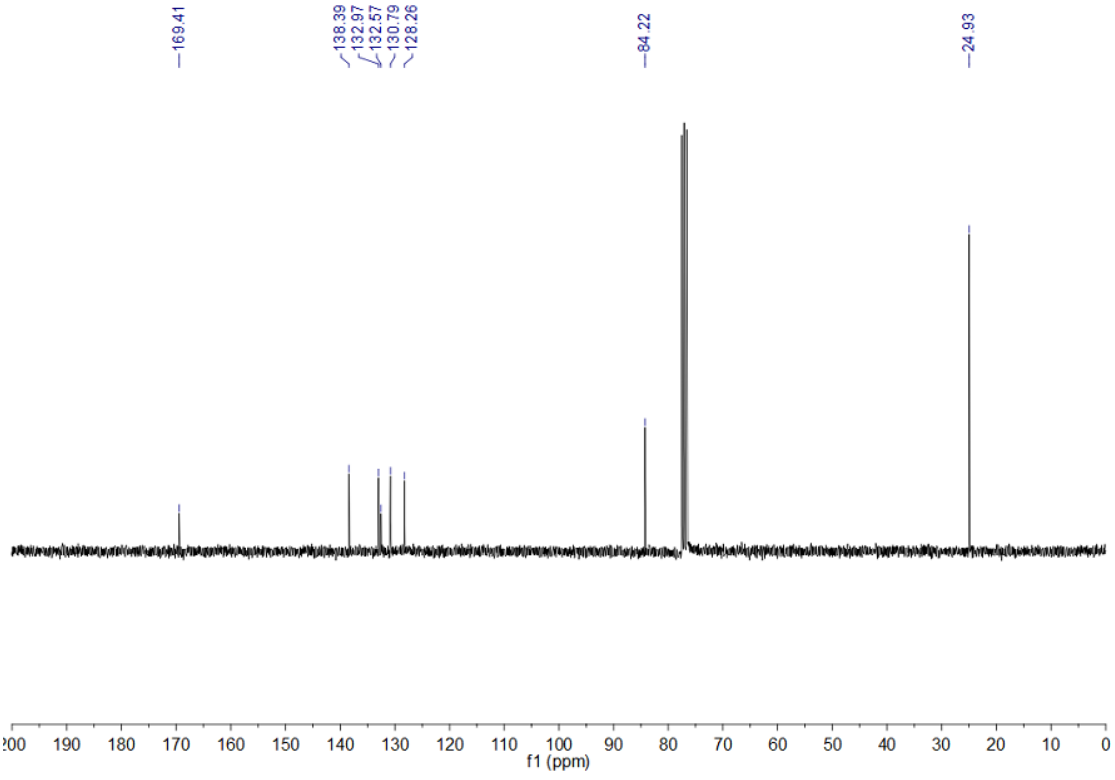




Entry 2 Table 4.10 Compound 4.20





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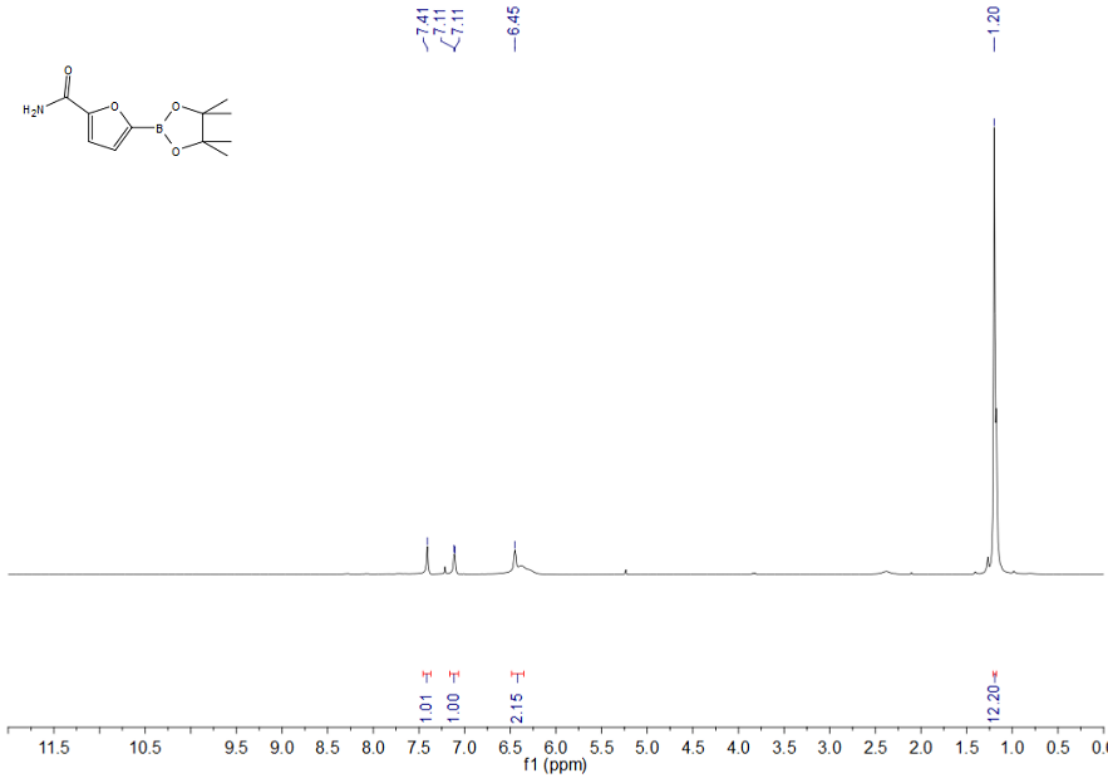
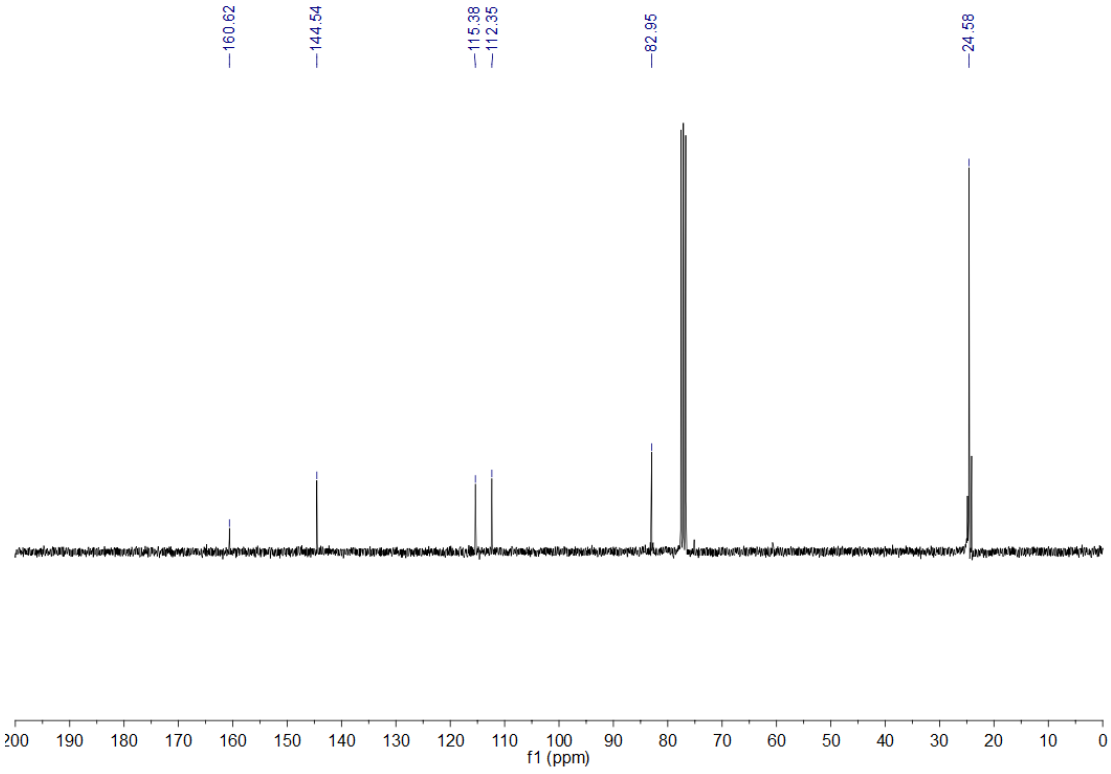
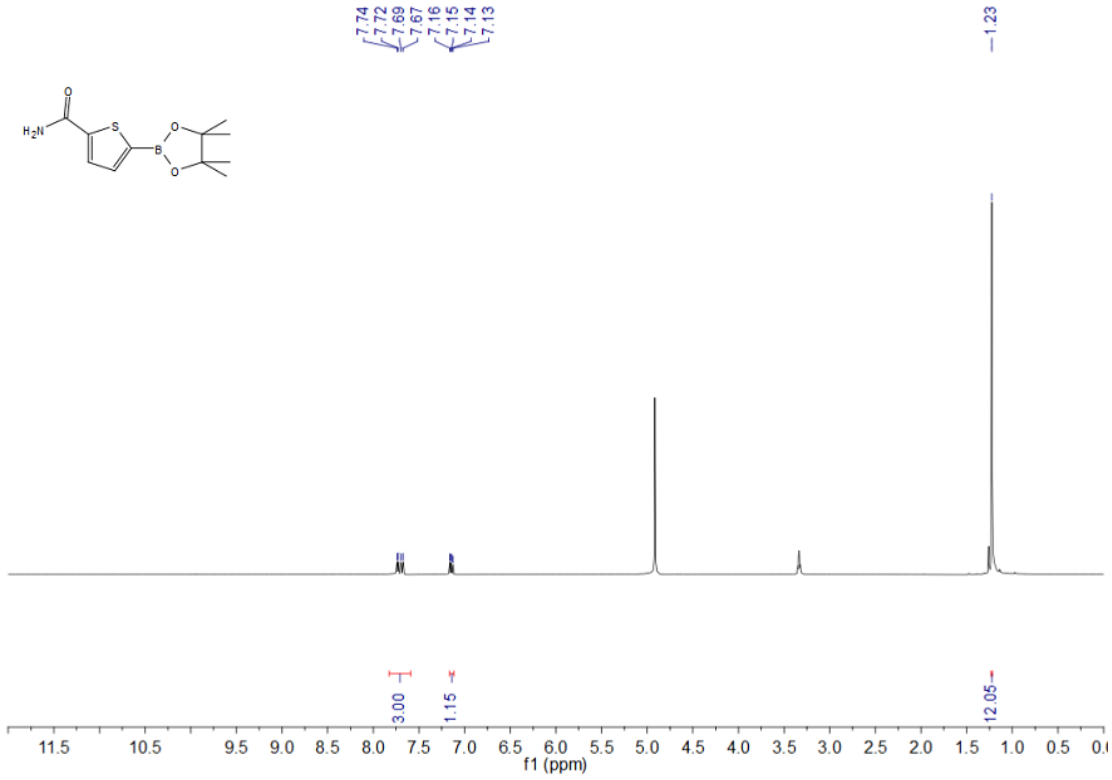
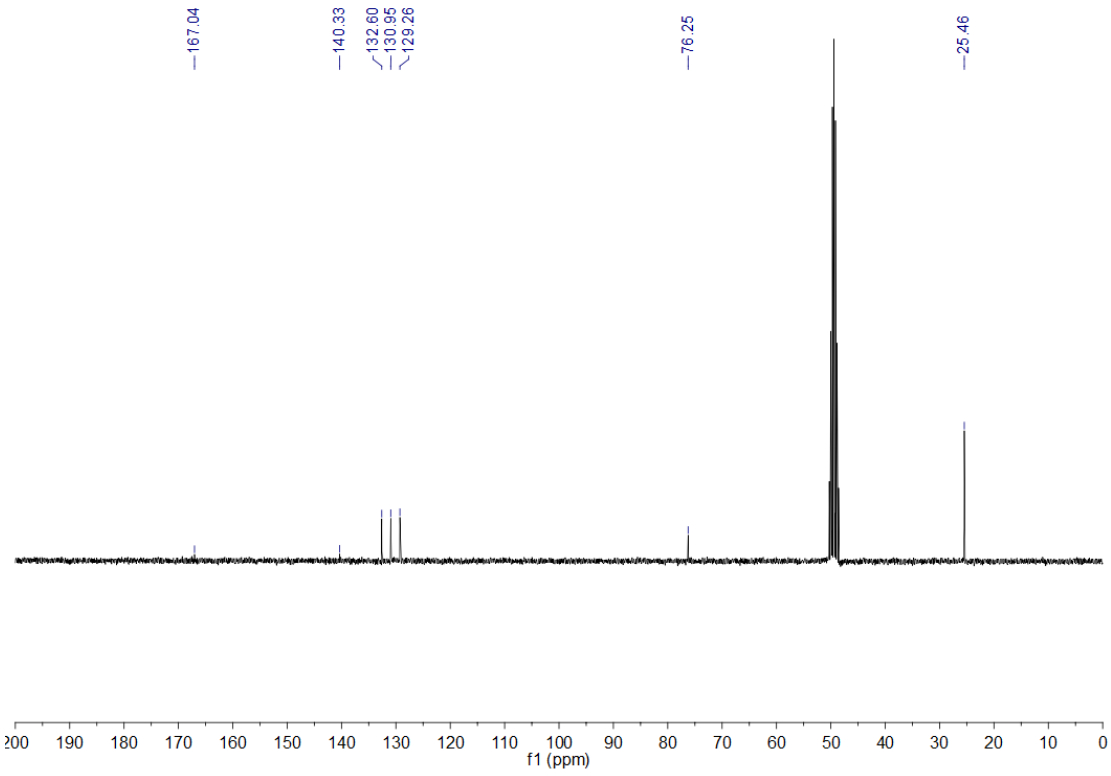




Entry 5 Table 4.10 Compound 4.23





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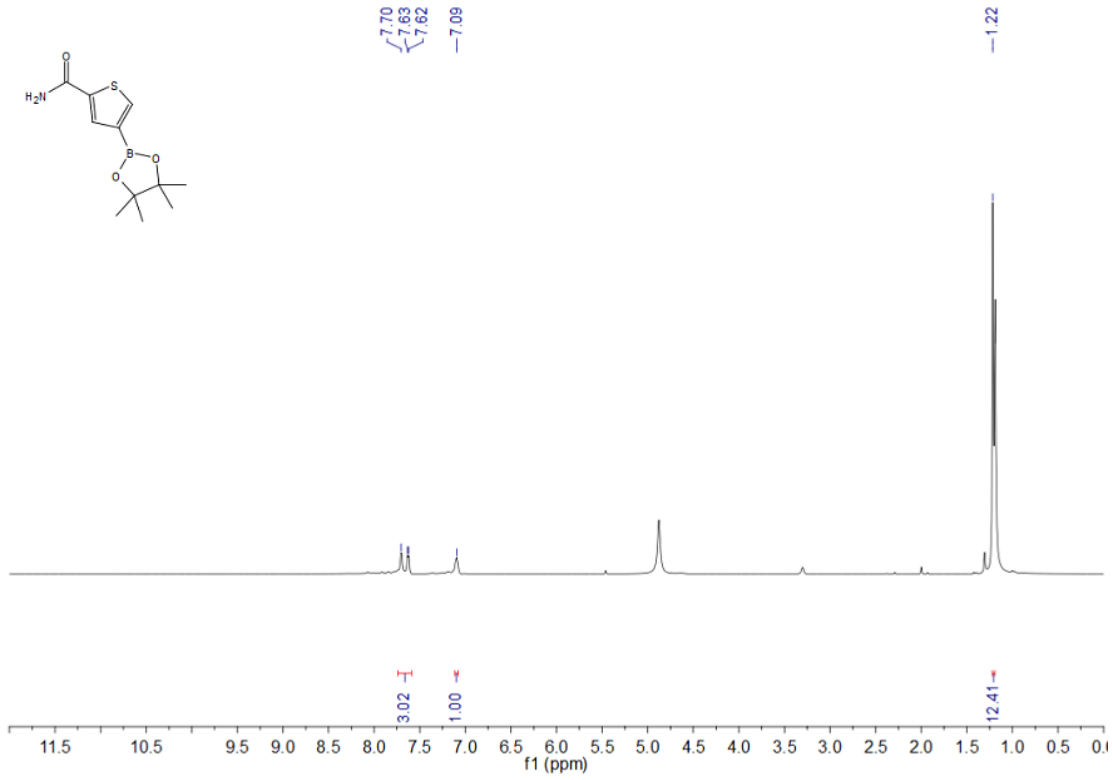

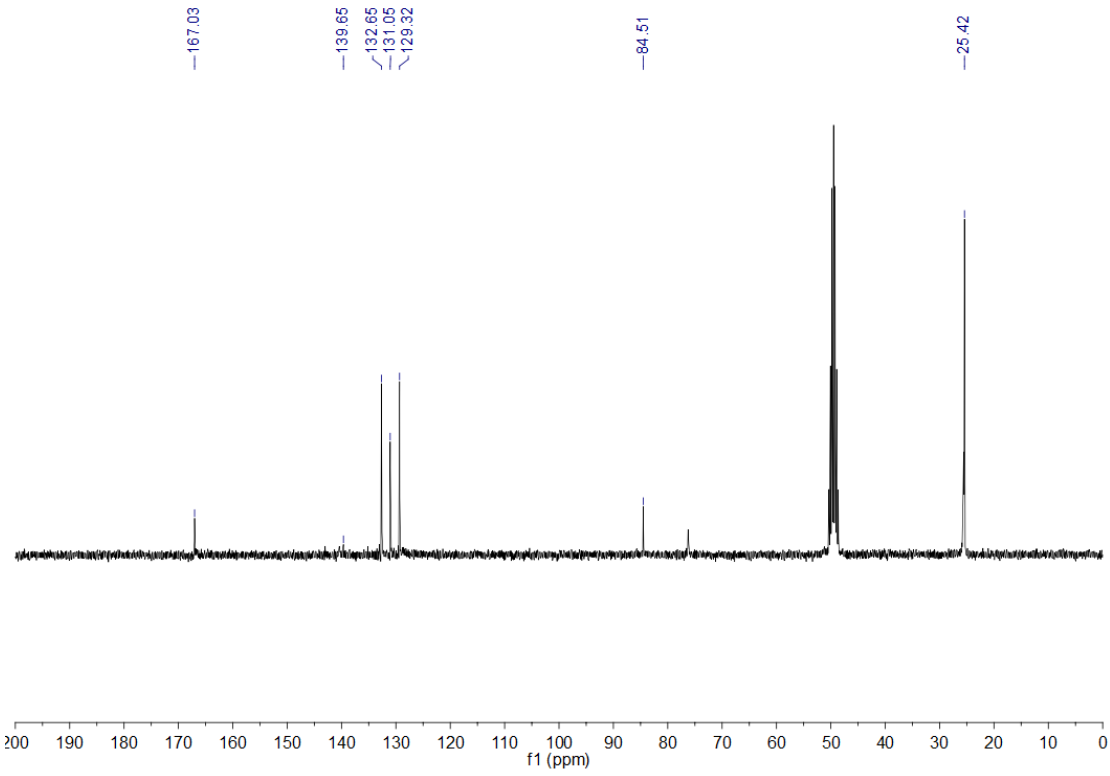

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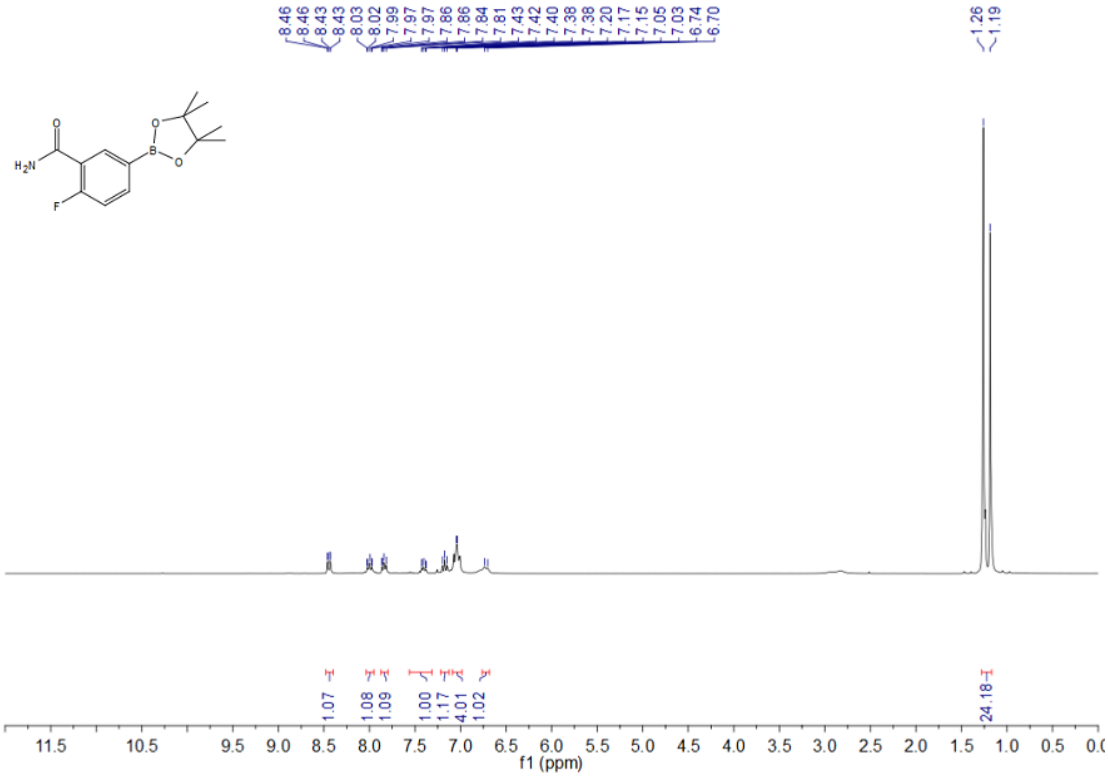

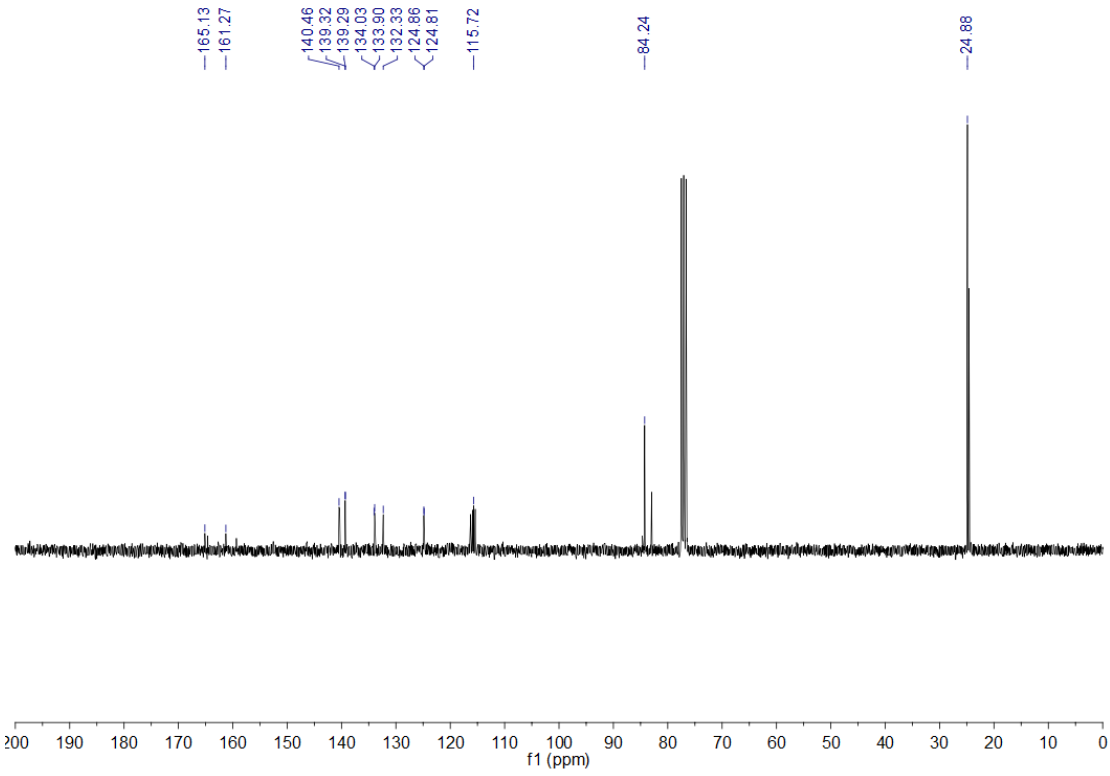

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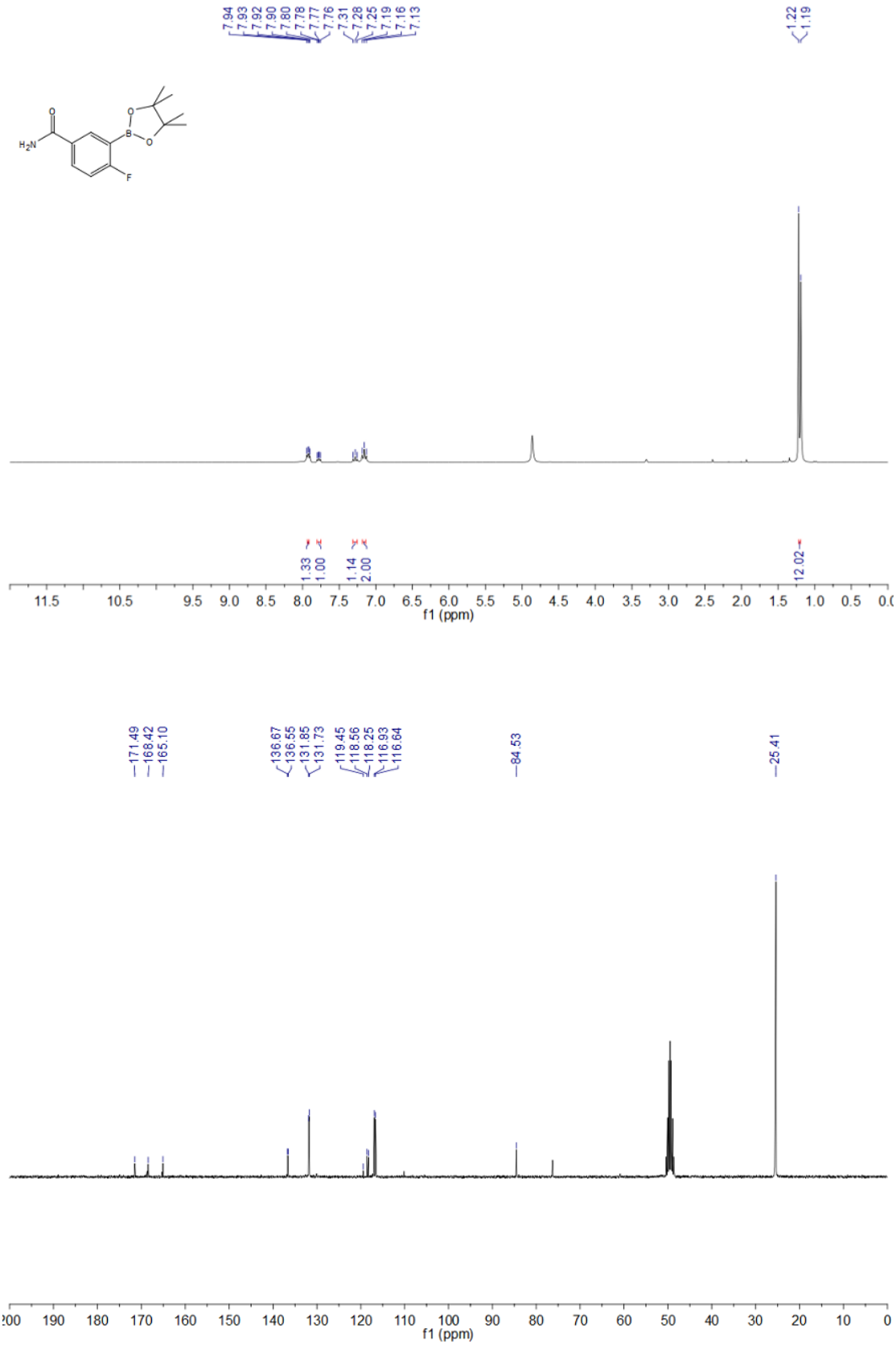
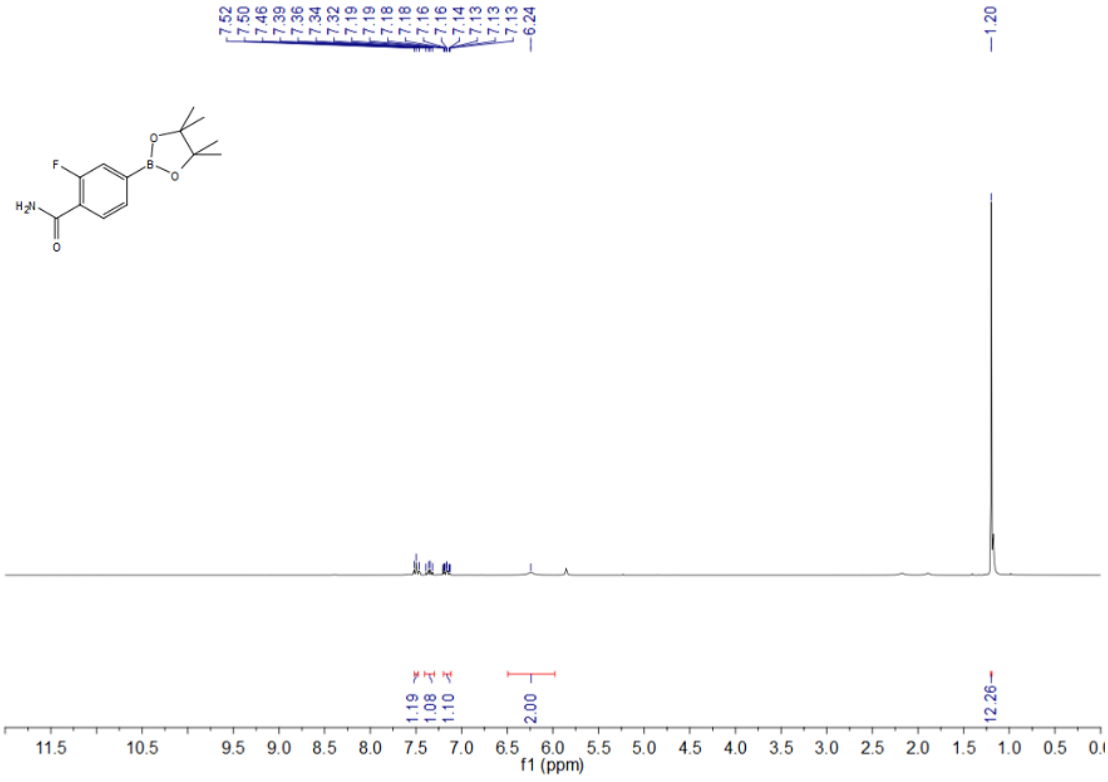
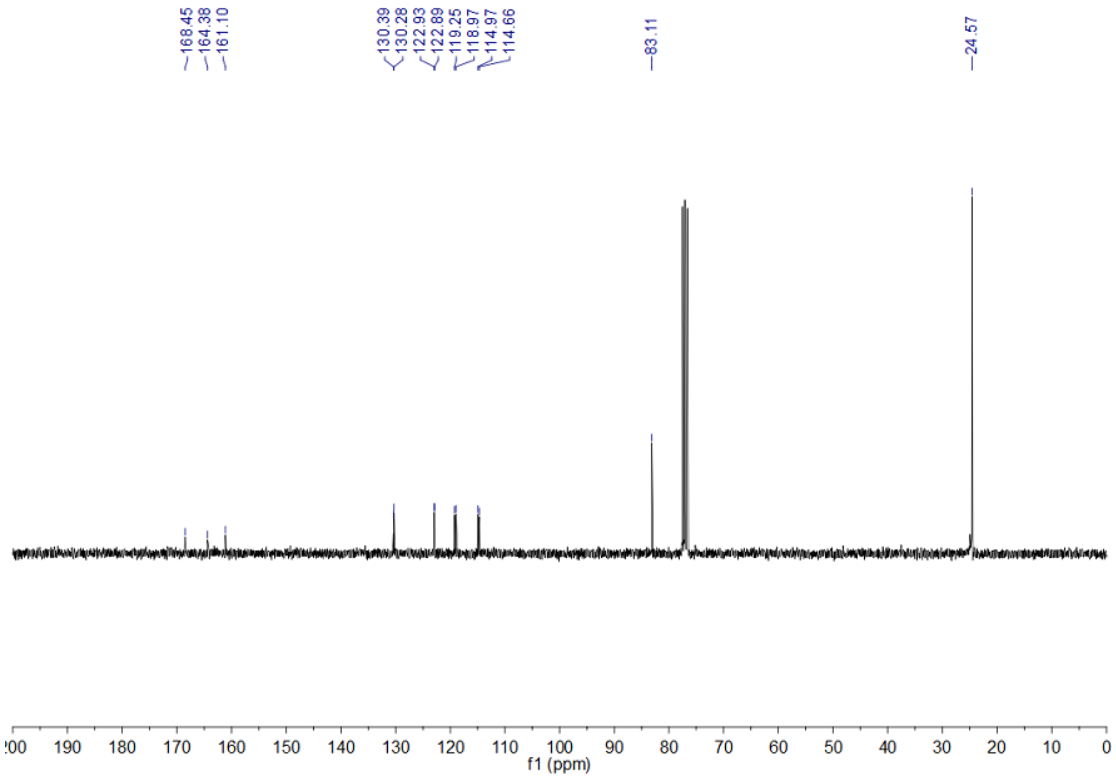


Entry 9 Table 4.10 Compound 4.27





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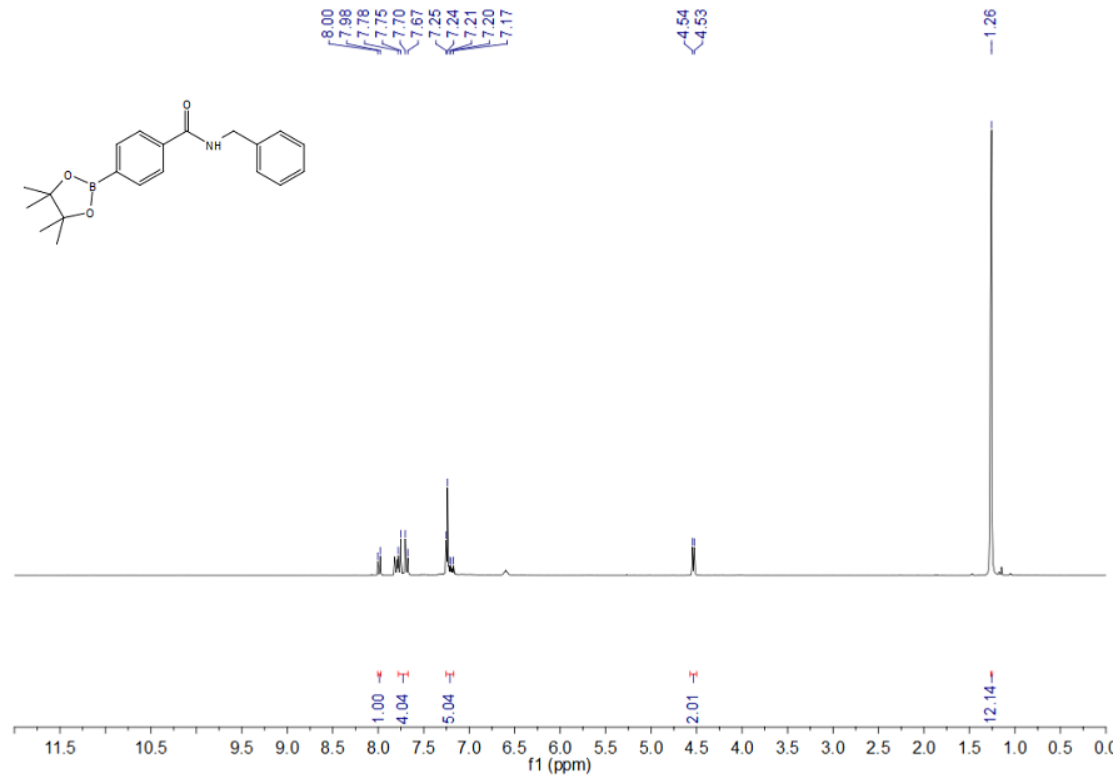
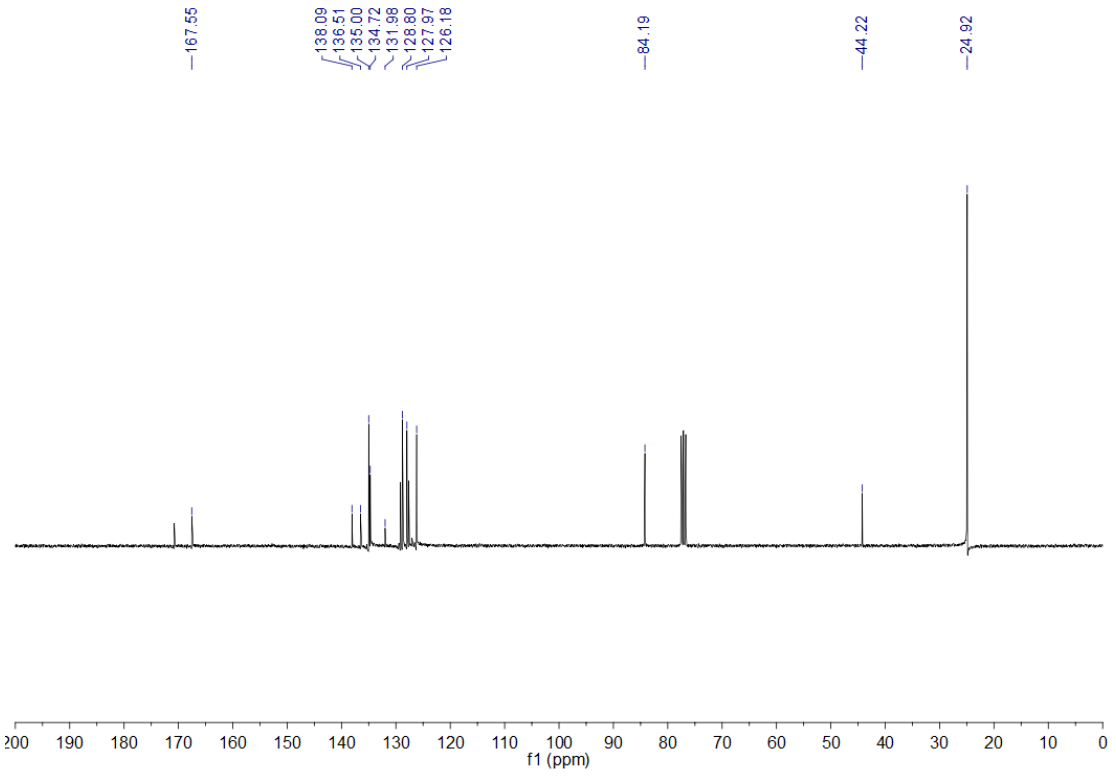
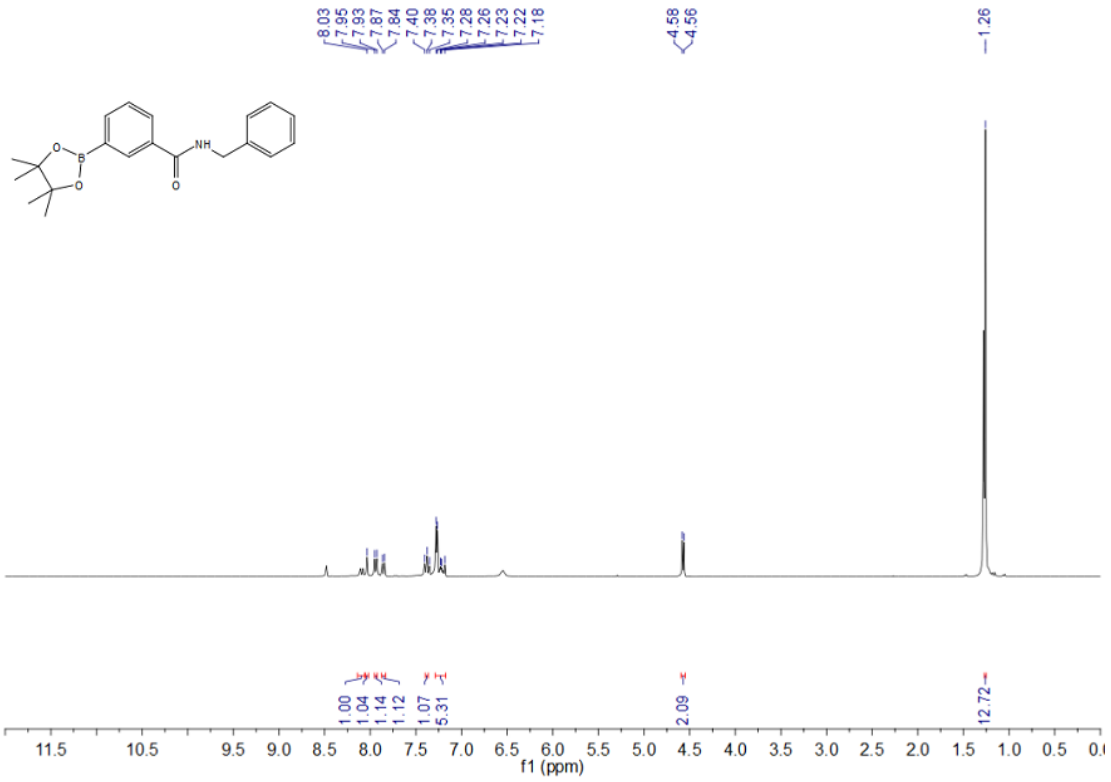
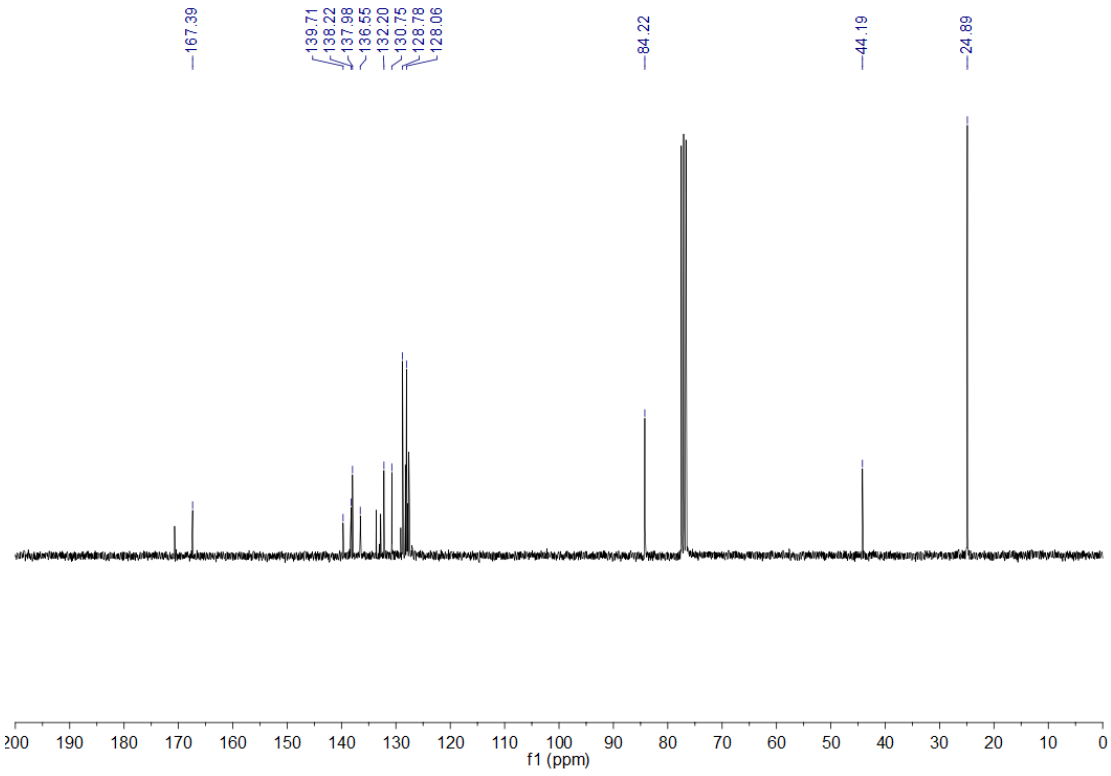




Entry 2 Table 4.11 Compound 4.31





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